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TEXAS REPORTS ON BIOLOGY and MEDICINE

Volume 1, Number 1 — Spring, 1943

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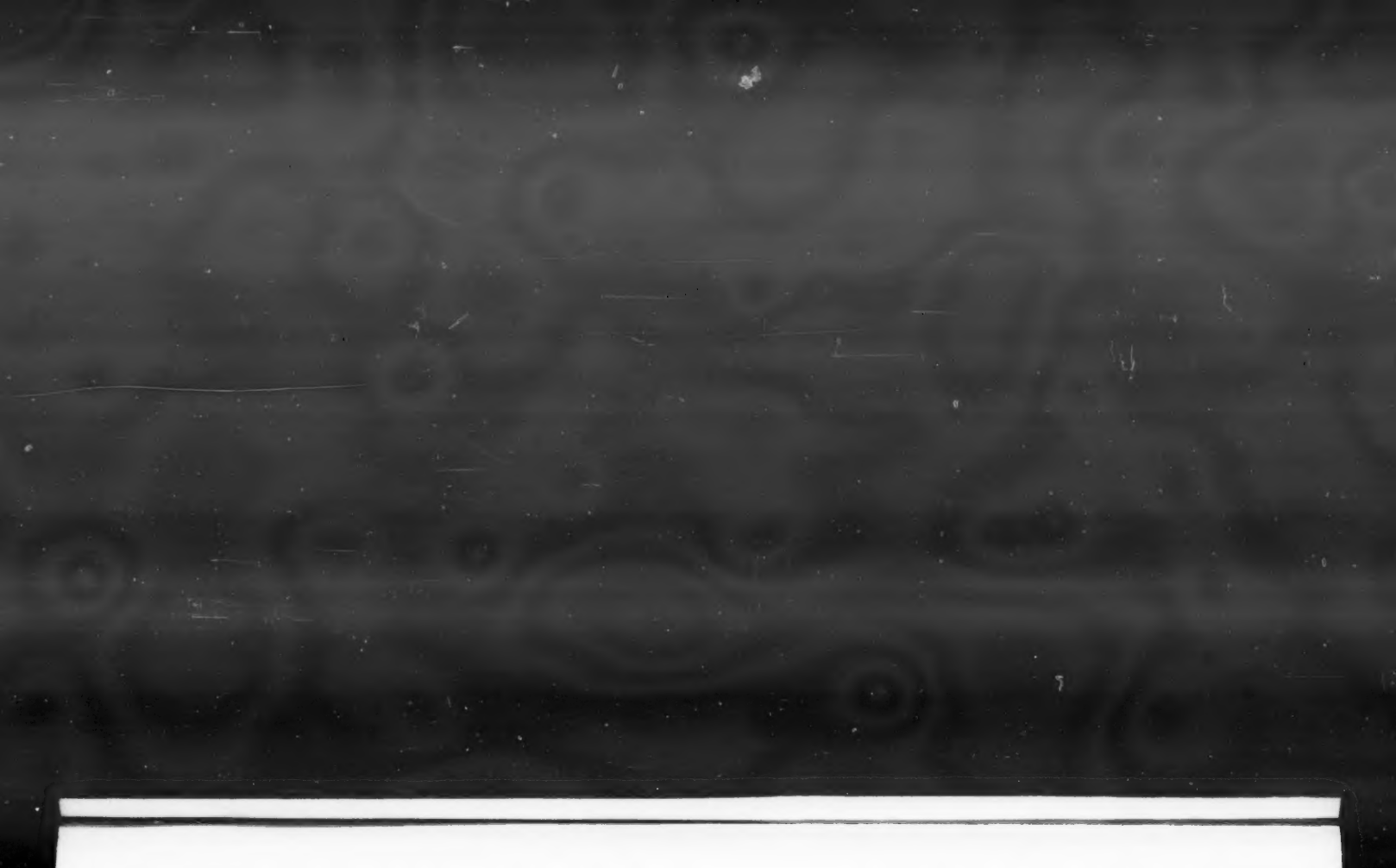

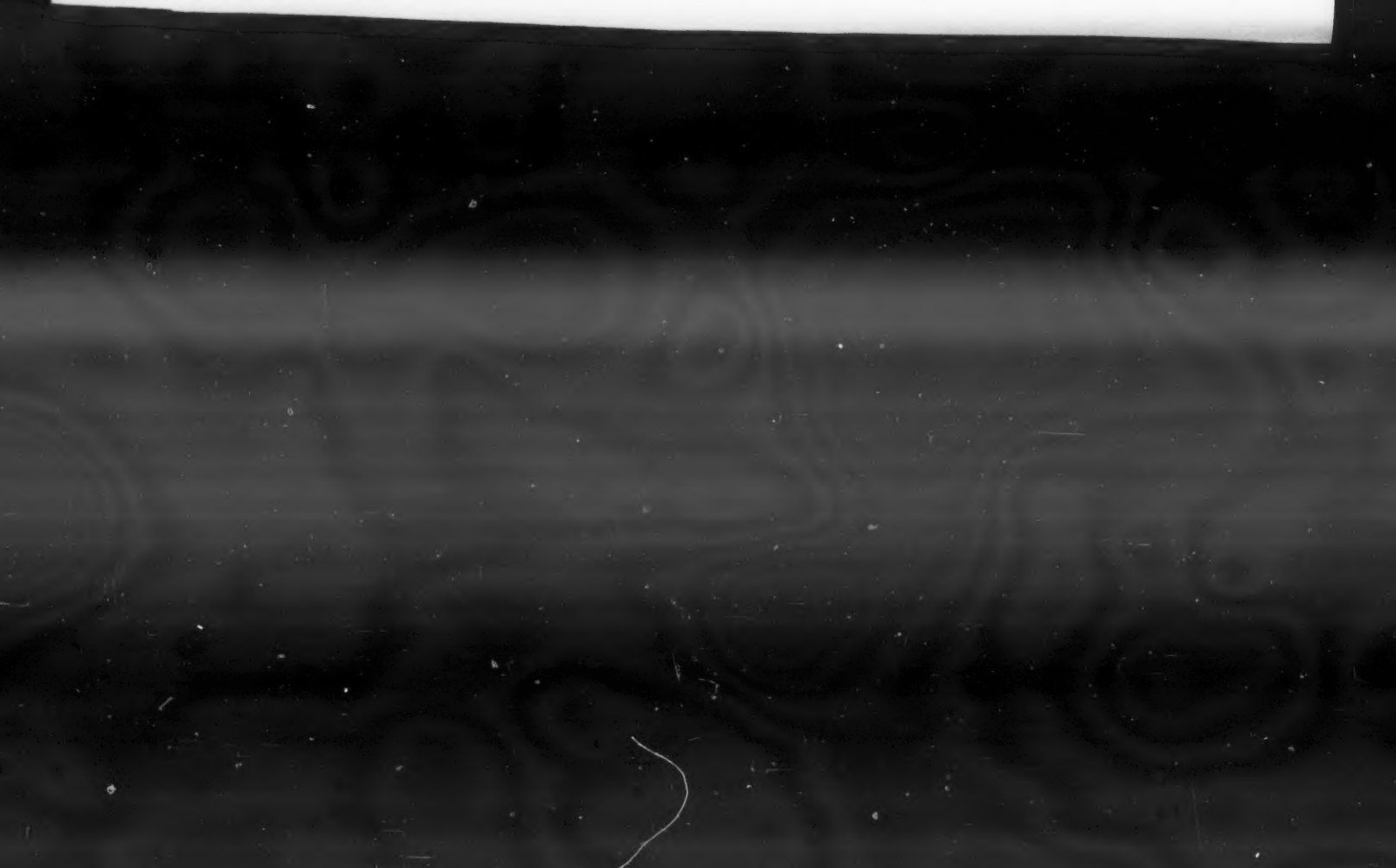

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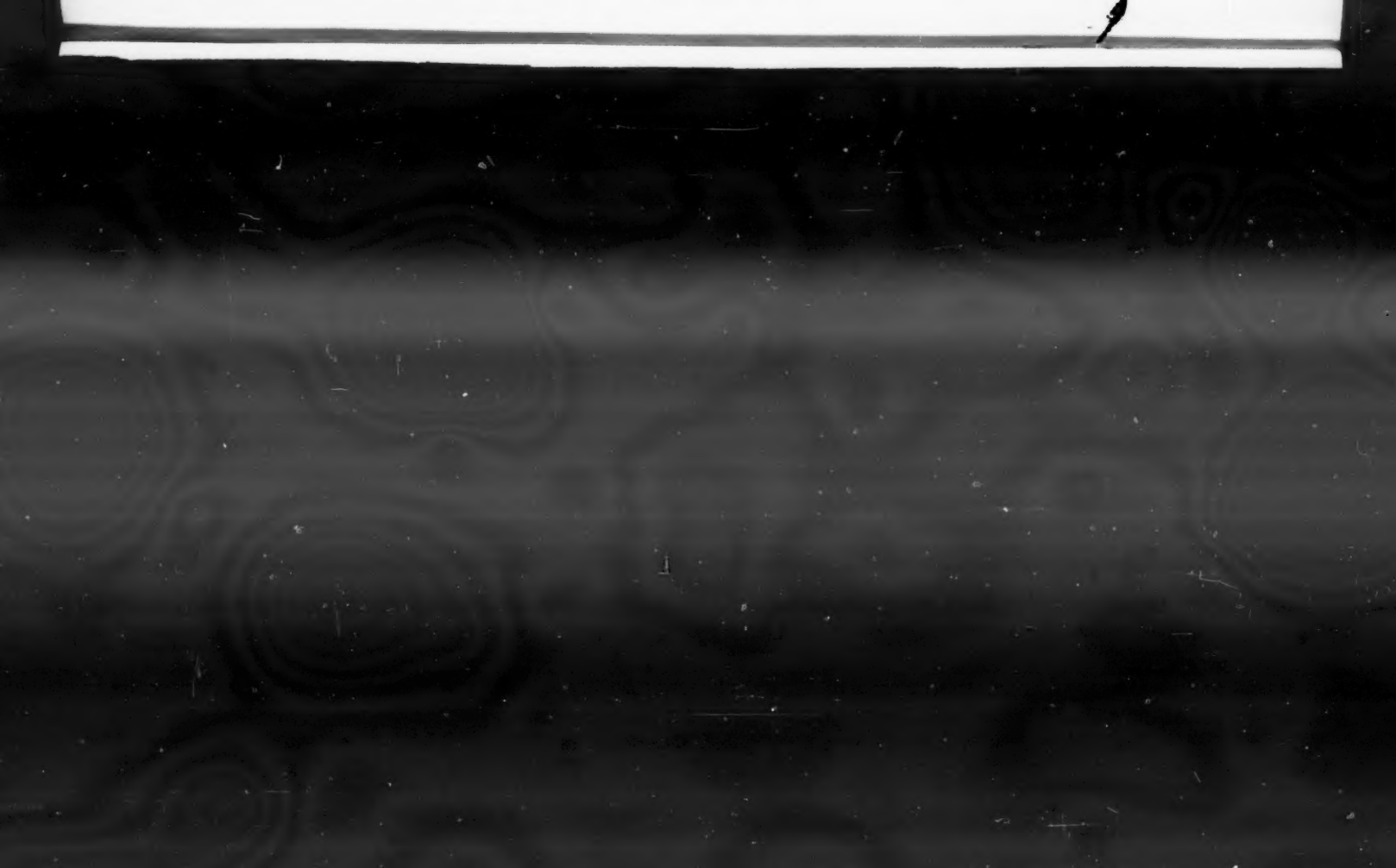
IN THE HALL OF THE LABORATORY BUILDING, UNIVERSITY OF TEXAS MEDICAL SCHOOL, DECEMBER 18, 1942
CLINICAL WAR SESSION, SEMI-CENTENNIAL GRADUATION EXERCISES

Edward Randall (of the original faculty); Col. I. S. Ravdin (Prof. Surg., Penn.); C. D. Leake (V.P. and Dean); Col. F. Ebaugh (Prof. Psychiatry, Colo.); A. Ochsner (Prof. Surg., Tulane); C. C. Sturgis (Prof. Med., Mich.); Com. J. C. Taylor (Pres. Texas State Med. Soc.); F. C. Elliott (Dean, Texas Dental Col.); E. H. Cary (Prof. Ophth., Baylor); O. Bullington (Regent); A. J. Carlson (Prof. Physiol., Chicago); Homer P. Rainey (Pres. U. of Texas).



TEXAS REPORTS ON BIOLOGY AND MEDICINE,
being
REPORTS FROM THE JOHN SEALY HOSPITAL
and the
UNIVERSITY OF TEXAS SCHOOL OF MEDICINE, GALVESTON

Sporadically during the past few decades there has appeared a monthly *Bulletin of the John Sealy Hospital.* This received generous support from the Sealy and Smith Foundation as well as from the Regents of the University. Designed chiefly for alumni and local interest, it contained case reports, occasionally scientific articles, and clinical reviews. It became increasingly difficult to support the effort as a monthly, and it ceased to appear after December 1939.

Local pride now proposes a quarterly publication from the John Sealy Hospital and the University of Texas School of Medicine. This new effort is planned more broadly to include various phases of biological investigation, particularly when they may relate to significant application in medical practice. It is hoped that the new quarterly may be of sufficient importance to attract the best contributions from any one associated with the University of Texas in relation to biology and medicine.

Highly significant studies are in progress not only at the Medical School Campus in Galveston, but also at the M. D. Anderson Hospital in Houston, and on the Main Campus at Austin. It seems appropriate that an opportunity be offered to publish the results of these studies under local auspices. This is a matter of increasing importance, since many of the national journals are restricted in editorial policy.

Texas Reports on Biology and Medicine is to be published quarterly, and is to be distributed without charge to every medical library throughout the world to which it may be possible to send it. It will also be distributed without charge to alumni. Libraries of medical institutions who do not receive it, and who may wish copies, should write at once to obtain them.

While a regional scientific publication of this sort may be expected to reflect local interest, the current trend of sci-

entific investigation in medicine is so wide that even local efforts may be expected to contribute to a broader picture. The free dissemination of accumulating knowledge is one of the important factors in the development of the free science of the world in which we believe. It is our hope that *Texas Reports on Biology and Medicine* may play a part in this development.

THE SEMI-CENTENNIAL GRADUATION EXERCISES OF THE UNIVERSITY OF TEXAS SCHOOL OF MEDICINE

The first students to graduate from the University of Texas School of Medicine in Galveston received their diplomas in June, 1892. Fifty years later on Friday, December 18, 1942, a special war program was arranged for the Semi-Centennial Graduation Exercises. The program for this occasion is reproduced on the following pages.

A feature of the Semi-Centennial graduation exercises was the special clinical war session arranged during the day. Distinguished leaders in various fields of medicine participated in this session. Some of the addresses delivered on this occasion are published in this issue of *Texas Reports on Biology and Medicine.*

SOME OBSTACLES IN THE PATH TOWARDS AN OPTIMUM DIET

A. J. CARLSON*

War, by interference with agriculture and commerce, as well as by direct destruction of foods, brings on starvation and the hosts of human ailments that sprout on malnutrition. Hence, in a world wide violence, like our present war, the ancient problems of individual and national diets requisite for health and efficiency become both a national and an international concern of nutrition experts, physicians, statesmen, and captains of industry. These imperative problems compel the biologist to re-examine the known and the unknown in the field of food and fitness, food and life, food and victory, so that the obstacles in the path towards an optimum diet for optimum health may not trip us in the dark. Such re-examination of the nutritional history of man (and other mammals), past and present, reveal as of today much new and reliable information, much innocent ignorance, many faulty food habits and unwise individual and commercial food practices of today, unwise practices in the light of present knowledge and past experience. There appear to be even questionable building stones in our scientific edifice; such dilemmas as the recent assertion by Surgeon General Dr. Thomas Parran of the U. S. Public Health Service that, in our own country with its abundance of excellent foods, and in times of peace, "one-third of our people is getting food inadequate to maintain good health, and less than one-fourth of the American people are getting a good diet." This is perplexing, especially in view of the more recent assertion (Nov. 1942) of Sir John Boyd Orr, Director of Great Britain's Imperial Bureau of Nutritional "There is no sign of malnutrition in (England and Scotland)." In fact, Sir John states that the people in England and Scotland are fed better in war than in peace, the people in the higher income brackets now eating one-third less than before the war, and those with lower incomes are now provided with better foods. Whether or not the alarming assertion of Dr. Parran as to the American people, and the optimistic statement of Sir

* Hixson Distinguished Service Professor of Physiology, University of Chicago. Read at the Clinical War Session of the Semi-Centennial Graduation of the University of Texas Medical School, December 18, 1942.

John as to Great Britain will stand scientific scrutiny may be partly a matter of definitions. But, unfortunately, these are not the only questionable stones in our edifice. We, we actual workers in the field of human health and nutrition, have, in most cases unwittingly, contributed many more.

The obstacles in the path towards an optimum diet are numerous. A good or an adequate diet may be defined as the kind and quantity of food which sustains the health and general efficiency of otherwise normal people at different ages. This is of course a rough overall estimate since we have no accurate quantitative measure either of health or of physical and mental efficiency. An inadequate diet obviously is the kind and quantity of food that induces physical or mental impairments measurable by our present methods. An optimum diet implies much more than this. It might be defined as that kind and quantity of food which permits and promotes optimum resistance to disease, optimum conservation of the factors of safety and powers of repair, and optimum length of life with optimum efficiency within the framework of the heredity potentialities of the individual and the species, and under the handicaps of the sequellol of accidents and disease. In enumerating and discussing some of the obstacles still in the way of securing or using such a diet for men, I wish to make it perfectly clear that the order of their listing does not in any way imply their relative importance. This we do not know, Colleagues working in the different fields will obviously rate these obstacles in very different order of importance but this is of little significance since many of them overlap, and provided that we recognize them all as actual or possible factors.

LACK OF KNOWLEDGE.

(A) If the above definition of an optimum diet is accepted, it will be clear to most informed people that the sciences of physiology, nutrition and medicine do not today have succifient knowledge to outline the components of an optimum diet. We do not know the optimum heredity potentials of any one individual. We do not know the tissue reserves that anyone starts out with at birth, nor do we have accurate measures of the depletion of these reserves until well advanced in the form of demonstrable or recognizable disease. We do not even know all about the optimum soil fertility for the production of grains, vegetable and fruit of optimum

nutrition value. In experimental nutrition in animal husbandry the rate of growth, body size and body weight, are usually taken as a measure of superiority of diet within the framework of hereditary potentials and in the absence of recognizable sequellol of disease. But one may question whether the height and other dimensions of men are adequate measures of an optimum diet so far as these elements are determined by the diet. I know of no evidence that the five foot ten inches individual is biologically, mentally, and economically, or even socially inferior to a six-footer. In some biological factors man is inferior to the gorilla, the tiger, the elephant and the horse. Yet he has survived and may some day conquer the jungle. The measure of biologic fitness of the man of tomorrow would seem to be *the capacity to produce, serve, and survive in the kind of environment worthwhile for men to live in.* It seems probable that in this task the size and plasticity of the brain is of more significance than the length of the legs or the width of the shoulders. The eight foot seven inch "Alton (Illinois) Giant" died at 22. At any rate the dinosaur and the mastodon are extinct but the ant carries on. We do not even know whether the eating of proteins considerably above the minimum requirements for growth, tissue repair and nitrogen equilibrium, is biologically indifferent or whether it improves or impairs mental and physical performance, whether it shortens or lengthens the life span. It seems clear, at least to me, that there is a large territory of unknown factors yet to be scientifically explored before we can talk with any degree of certainty about an optimum diet for man. Therefore those who know the most in this field ought to confine themselves for the present to such terms as good or adequate diets, on the positive side. If a good diet, or even an optimum diet alone was omnipotent and could push back the hereditary limitations of the individual we should not so often see differences in physical and mental capacities of children in the same family at least not in the absence of accidents of non-dietary diseases. If a diet of "red meat" alone was the determining factor on the football field there would be no scores on either side, outside of accidents and luck. Genius, like mortals made of common clay, can neither develop their best nor for long balance on a top rung of the ladder on seriously inadequate diets. It seems equal-

ly certain that even optimum diets will not build genius out of all clays. The persistence of hereditary factors and the unknowns of mutation appear to say that much.

Drs. Park and Follis, Jr., of John Hopkins Medical School, have kindly put at my disposal their results to date of their significant and long study on the prevalence of rickets in the bones of 230 children between the ages of two and thirteen years dying of sundry acute and chronic diseases, primarily of non-dietary origin. They find signs of rickets in 46½ per cent of these children. The acute diseases ending some of these children's lives appear to be of too short duration for the disease itself to have been the primary factor in the initiation of rickets although the disease might have aggravated the rickets. It is doubtful that the conditions of rickets in these children could have been diagnosed without this type of examination after death or by biopsies of the bones during life. In my judgment this is a significant approach towards the study of incipient dietary deficiencies and a commentary on the society of today in failing to apply the known, for we have known for many years the dietary requirements for the prevention of rickets in the absence of disease.

Our knowledge of the composition of foods, the role of foods in the living body and the specific requirements for the main groups of foods in the living organism—the proteins, fats, starches, inorganic salts, and vitamins—have increased enormously in the last fifty years. This detailed knowledge has, however, not gotten down very effectively to the man in the street, the woman in the average home, or the people in the factory and on the farm. More recently, the startling character of these biological and chemical discoveries in human nutrition has, to my way of thinking, led to much unfounded anxiety, fear, wishful thinking, and questionable commercial exploitation.

Whether or not we can maintain good health on 40 grams or on 100 grams of protein per day depends largely on the kind of proteins we eat, as the biologic or nutritional value of proteins differs greatly. Some ten so-called essential amino acids are now known. These protein "building stones" are so called, because the human body cannot make them from the other nitrogenous elements in the diet. How-

ever, these essential building stones are present in varying amounts in nearly all proteins of animal and vegetable origin. Man's past history teaches us that if we eat a sufficient variety of natural foods, we will get all the essential amino acids needed for good health. Meats, milk, eggs and grains provide good food proteins. The first principle in adequate dietary proteins is accordingly: *variety, natural foods, omnivorousness.*

Up until yesterday even experts in nutrition thought that the nutritive significance of the animal and vegetable fats in our dietary, besides providing flavor, was: (1) energy or calories, and (2) carriers of such dietary essentials as vitamins A, D and possibly others. It now seems highly probable that two or three of the numerous fatty acids in the animal and vegetable fats are as necessary in our diet as are the essential amino acids of the proteins. But, as in the case of the proteins, nutritional welfare of men lies in variety and omnivorousness, since these essential fatty acids occur widely in plant and animal fats.

(B) It is almost superfluous to point out that many diseases, acute and chronic, not primarily of dietary origin, may and do prevent, in part at least, the good effects of good diets. The infant with summer diarrhea no matter what food is given does not get the full benefit of that food. This applies to many diseases of adults. In the presence of hookworm infestation good foods alone does not seem to engender maximum physical and mental efficiency. Chronic lead poisoning in the child appears to so interfere with the use of the calcium and the phosphorous in the diet as to induce or aggravate the disease of rickets. We are not now concerned with the important problem, the role of a good diet in the prevention or limitation of infectious disease. Diet alone does not seem to promise the conquest of infections. But when we speak of good or optimum diets for the entire population of the land we must keep in mind the non-dietary disease factors that nullify in whole or in part the good results seen from such diets in individuals having these diseases.

FOOD HABITS.

(C) The food habits of man tend to become as fixed and in many cases as unreasonable as many of his religious, political, and social habits. The name of foods, the visual appearance of foods, as well as the taste of foods are frequently determining factors. The consumption of types of foods by people or races less sophisticated, more ignorant or poorer financially than we are—such foods are frequently looked upon by us as degrading, or not good for us. Many people refuse the meat of eels because this fish looks like a snake. Many people think that food good for dogs, cats, and hogs are by that token not good or fit for man. A control factor here is obviously social habits as well as the fact that we can train our palate to like or prefer even foods markedly deficient in some of the dietary essentials. For example, the liking for sugar, sweet drinks, candy. Now sugar is a good energy food and such preference for sweets is not serious provided we eat enough of more complete foods. But when foods like pure sugar or pure starch become a large percentage of our daily diet trouble will follow.

Wherever we turn in the dietary field, past and present, there appears an important factor of safety in *omnivorousness*. Very few of the natural foods contain chemical or organic poisons for men. Civilized man could be even more omnivorous than he is at present, but we do add serious chemical poisons (lead, arsenic, fluorine) to some of our very important if not necessary food categories, fruits and vegetables. To be sure these insecticides are sprayed on important human foods, not with the intention of injuring man but for the purpose of rescuing good human food from insects. However, one of the dietary unknowns to-day is this: How much of these protoplasmic poisons we can take with our fruits and vegetables during the lifetime without impairing our reserves, impairing our health? The consumer demands a perfect apple. We can see the "worm" or the track of the "worm" in the apple. The lead, arsenic, and fluorine on the perfect apple we either cannot see, or when we do see them we think it is more dust from the good earth. We should like to know whether the dietary health of our forebears was worse off with a worm in the apple, than is ours.

Modifying human food habits in the direction of better health and efficiency may come through necessity or dictation. It will probably not stay put except through understanding via the long and strenuous road of education.

In the matter of education in health to the extent that our health depends on food I think there is much yet to be done in our grade schools, high schools and colleges. In a not too distant past the teaching of health in our schools did not significantly transcend the tooth brush, alcoholism, sex and social diseases. Even today in many of our schools we find inadequate teaching of the fundamentals of health and nutrition. As if the matter of foods was a concern for women students alone and the matter of general health a concern only of the physicians.

We have scarcely begun to realize that the modern sciences of chemistry and physics are so rapidly changing our environment and mode of life that proceeding today in the ignorance of our forbears we may travel into tragedy. Urbanization and industrialization renders it well nigh impossible for modern man to have access to the natural unprocessed foods avialable to our forbears of a thousand years ago.

FOOD ADVERTISING.

(D) In connection with this discussion of the education of the public in health and foods one necessarily thinks of the positive and valuable role that modern commercial food advertising could play in this program. Unfortunately such commercial food advertising in the past has frequently been misleading and occasionally undiluted but artistic lying. People are urged to eat more of everything. If they could do that very thing they certainly would develop dangerous obesity. The 1942 advertising of a vitamin alleged to prevent or recolor gray hair on the human scalp is as yet without foundation in science. There are cheerful signs now that the more responsible food producers and food processors are being aware of their public responsibility in this field. Their responsibility is contributing to factual adult education as to food and nutrition in advertising their special ware. But it is discouraging to say the least, to have our federal government leaders urge us (in posters, advertisements and circulars): *"Eat Nutritional Foods."* This is silly, and, if certain foods are listed to the exclusion of others,

misleading. For an article which is not nutritional is not a food.

(E) Food refining and food processing may impair the value of foods. These are numerous, such as polishing of rice, the milling of the germ, and much of the protein vitamins and inorganic salts out of such foods as wheat and other grains, corn, etc. Purification and hydrogenation of animal and vegetable fats may take considerable if not all of the fat-soluable vitamins out of these fats. Modern preservation of food such as canning, freezing and dehydration is necessary in modern urbanization. Some food values are diminished unavoidably by these processes. Cooking, freezing and packing undoubtedly saves man from infectious disease but some food values are lost. It is a question of balance of benefits. Fortunately we do still eat raw fruits and some raw vegetables. The latter could and should be greatly extended.

Digestible carbohydrates occur usually in abundance in most of our natural foods. Except by heat to point of carbonization these foods factors are not denatured or destroyed by food processing, baking or cooking, except that the sugars and water soluable starches may be lost into the cooking and canning liquids. Dextrose, the sugar of the blood, is a necessary constituent for our internal environment. A large part of our heat and energy requirement can and should come from the starches. The starches are our most easily digested and on the whole the least expensive energy foods. So necessary is our blood sugar (dextrose) that, as in prolonged fasting, the body appears to manufacture it from body proteins, and possibly from the body fats. It now seems clear that our body can do the same with the proteins and the fats of our common foods. Hence no specific or distinct dietary deficiency disease of man is known as due to too little starch in the diet. A form of mulnutrition, obesity, may be caused by eating too much starch, or sugars, as the carbohydrate in excess of our energy needs is readily converted to and stored as body fat. However, some of the important dietary deficiency diseases have come about, not by eating too much starch, but eating too little of the other important elements in the natural grains. I refer to the polishing of rice and the modern milling of wheat and other cereals for white or patent floor. The germ and the outer coats of the grain holds valuable proteins, vitamins, and min-

erals. Human dietary safety on this front would seem to be: go back to first principles, *putting the whole grain into the flour of the bread.* This can be done. We can learn to like it. If Great Britain (at war) can take an important step in that direction, why can't we? Fortunately, we still eat oatmeal, a whole grain food, having among other valuable nutritients, proteins of high biologic value.

I believe we could learn to prevent the oxidative rancidity of whole grain flour. If we insist on milling the grain and storing the flour, instead of storing the grain, and milling as needed, there are now known relatively non-toxic antioxidants to prevent the rancidity of whole grain flour that takes place on long storage. And until we have that problem licked, what is the matter with storing the wheat and milling the flour as we need it? I do not see any essential economic principle in storing the flour in place of storing the wheat. In my judgment, the recent addition of a little of the vitamins and minerals now milled out of the grain, and singing paeans of dietary salvation over this "enriched" flour and bread is not a sound policy either for today or to-morrow. Let us go back to first dietary principles on this front. The whole wheat, rye, oat, barley, corn and rice grain are among our most valuable and our least expensive protective foods. This is nothing new. We are told in the Book of Genesis: "Behold I have given you every herb—to you it shall be for meat." On the whole, we can trust nature further than the chemist and his synthetic vitamins. Recently Professor J. C. Drummond, the scientific adviser to the British Ministry of Food, voiced his reluctance to put the dietary safety of a nation on synthetic vitamins, as a long range policy. He thinks we must, and should, provide the natural vitamins in the natural foods. I stand on that platform, until we know a great deal more than we do today about foods and human nutrition.

It appears true that for our forbears, except for the element iodine in restricted areas of the earth, the dietary need of minerals was efficiently met by the common non-purified, non-processed natural foods. So far as I know, this would still hold true, except for the cooking of such foods as meats, fruits and vegetables, and the habit of discarding the cooking water. To be sure the otherwise excellent natural food, milk, is so deficient in iron that an exclusive diet

of milk for weeks or more, brings on an anemia due to the iron deficiency in the diet. How does the American dietary stand as to some of the essential minerals needs, such as calcium, phosphorus, iron and iodine? The iodine deficiency in the states whose soil and water were depleted of iodine by the waters from ancient glaciers is now taken care of by putting the iodine back into our table salt. The iodine was there before our ingenuous chemists learned to take it out. Professor C. H. Sherman of Columbia University, has long held the view that the American diet is probably too low in calcium, and possibly in phosphorus, for optimum nutrition. The problem is complicated by the fact that a modicum of vitamin D is involved in the adequate absorption and utilization of calcium and phosphorus, particularly in the growth and maintenance of our bones. *I wonder if the possibility of a dietary danger in this field could not be met, universally and without cost, by adding a little calcium, phosphorus, and iron, to our table salt.* This should offer no insurmountable difficulties, and there is no evidence that a slight excess about actual needs of these minerals works any injury to our health.

We are urged to eat milk especially for its calcium. Yes, milk is a good source for lime. But milk is a relatively expensive food, and even in our country, with a plethora of foods, there is not enough milk to go around, at least as long as we insist on butter and cream for our table, and turn so much (50 billion pounds a year) of the valuable skim milk into channels other than human food.

HOW MUCH VITAMINS DO WE NEED FOR GOOD HEALTH?

That the disease scurvy induced by prolonged subsistence on dried, cured and cooked foods, can be cured or prevented by eating some fresh or raw fruits, vegetables, potatoes, leaves, or grasses has been known for more than a hundred years, but the specific chemical substance involved (ascorbic acid or vitamin C) is of very recent acquaintance, and the precise role of this vitamin in our cellular health is still partly unknown. *Pellagra, beriberi* and *rickets* are old human ailments, but their precise etiology and partial conquest belong to the last fifty years.

The recent advances in our knowledge of the chemical nature and the biologic role of the vitamins have been so

rapid and so startling that, as usual, man's wishful thinking hopes to find in them the cure for nearly all the physical and mental ills to which the flesh is heir. In fact, the miracles now claimed by some misguided people for vitamin pills, natural and synthetic, rival the miracles of Lourdes. The giving a mixture of table salt, vitamin C, and vitamin B_1 to workers in very hot environments, observing reduction in fatigue and heat prostrations, and concluding that the vitamins contribute to this desirable result is not a scientific experiment. For we know that under such conditions NaCl alone produces these results, and it is difficult to measure fatigue with accuracy. Vitamin concentrates are useful aids in the hands of a physician. The tragedy and waste in the 1942 vitamin pill business is this: *most of the people who can afford to buy them probably do not need them; most of the people who may need them probably cannot afford to buy them.* But a competent chemist assures us that "intelligence and morality go together . . ." Since an ample supply of vitamins can foster a high intelligence, it has also the capability of fostering morality! If this be true, and if we further admit that lying and injustice are phases of immorality, the vitamin deficiency in the human race of our generation is indeed appalling! When we have the vitamins that prevent dishonesty and injustice, the millenium will have done. But as I read and listen to the 1942 propaganda for vitamin pills, I am led to suspect that at least some vitamin venders do not take their own medicines. They just sell them. And the selling noise is so loud that our attention is distracted from the more important role of adequate proteins in preventing one of the fundamentals in the overall malnutrition created by such catastrophies as crop failure and war.

(F) *Waste of Food.* Waste of food in the family increases the cost of food to the family. It also contributes to food scarcity. Food waste in our country is partly avoidable, such as the waste in the home, waste or neglect of fruit and vegetable on the farm, partly perhaps unavoidable such as that produced by oxidative rancidity of fats in the foods. I have already referred to the huge waste of skimmed milk, so far as this good food is turned into channels other than human food. The waste of food in the homes tends to increase with the economic prosperity of the family. It is not

"refined" to clean the plate. It is a measure of prosperity and caste to waste food. When we are told that under conditions of war and food rationing in England and Scotland the economically more fortunate eat one-third less food than they did in times of peace, this probably means that they eat just as much food in war as in peace, if they can get it, but in war, they waste one-third less food in the kitchen and at the table. When nations are facing universal food shortage, the wastage of food in the home or on the road from the farm to the home may seriously contribute to national malnutrition. Much of this food waste is even today preventible but, we are up against individual and social habits and agricultural practices that will yield only to education or dire necessity. Some food wastage in the home as well as in the food processing industry appear to be based in part on the erroneous assumption that the least roughage on the food that we eat the better for our health. So we peel and prune fruits and carrots, cabbage and potatoes and with such peelings and prunings we decrease or eliminate valuable food elements. The facts are the normal human alimentary tract must have some indigestible roughage to work at its optimum and it will probably take millions of years before man has evolved, like that of the honey bee, an ailmentary tract that can function on nectar and pollen alone. I am not aware that the roughage in the whole grain food, oatmeal, has damaged the alimentary tract of man. It is difficult to assess the blame for some of the waste of our food particularly the fats of animal origin. We seem to have developed the idea that the fattest hog and the fattest steer is the best hog and the best steer. These animals may be best in the sense of providing greater income to the farmer but a great deal of the fat of the steer and even some of the fat of the hog does not reach the human stomach. From the kitchen or dining table it passes into the barbage can or down the drain pipe.

(G) *Poverty.* Many people are undoubtedly inclined to put poverty as obstacle No. 1, even on the road to a good or adequate diet, not to say an optimum diet, and I am not quarreling with the relative importance of any of the factors, as I indicated in the beginning. Whatever the percentage of truth there is in the view that forty million, even a hundred million Americans are badly nourished, there can

be no doubt that financial handicaps may be serious enough to prevent the purchase and consumption of food adequate for good health. And even if one per cent of our fellow citizens belong in this category in this land of abundance of good foods, that would be a reflection on our knowledge, education, wisdom and competence. But among men as among animals below man, securing food without labor, without scratching, leads in the long run to biologic deterioration. Among the wants and fears of man in many lands are the lack of good foods and the fear of starvation. Sir John B. Orr, the British war time food administrator has recently proposed that this seemingly simple aspect of the "Atlantic Charter" should be our primary concern. But even this is by no means simple. For in absence of epidemics, all species, man included, tend to reproduce beyond the limits of an adequate food supply for all. So a necessary corollary to freedom from the want of good food, and freedom from the fear of starvation everywhere, is planned parenthood. To me at least, this seems as humans, reasonable, and necessary as our civilized and scientific endeavors to prevent and control the other form of universal human suffering disease.

The financially poor, the financially unfortunate appear to have been with us throughout recorded history. The common saying is: "The poor will always be with us." Maybe so, at least in a relative sense. For there is also poverty in foresight and poverty in individual endeavor. In so far as this is due to poverty in heredity, common sense seems to say that, as knowledge grows, we must apply new measures to decrease the production of the chicks that chirp but cannot or will not scratch. Unless reason based on understanding effectively guides social evolution of to-morrow in that direction, I see no escape from the degeneration that invariably follows biologic parasitism, except the ancient law of "tooth and claw." The killing of millions of pigs for fertilizer, and restricting the production of such important foods as meats, wheat and corn, all by Federal refulation, do not (in my judgment) square with our concern for an optimum diet of man (the poor included) even in our own land.

(H) *Appetite.* We know to-day very much less about the precise mechanism of appetite for food than we know about the mechanism of hunger, but stated briefly, appetite

for food in contrast to hunger does not seem to be primarily inherited. It seems to be a memory of previous pleasant experiences with foods, pleasant experiences in the sense of taste, odor and visual appearance of foods. One fact stands out clearly in the matter of appetite, and that is this: All normal people seem to be able to acquire a liking or appetite for any kind of substance that can serve the nutrition of man. This, I think, is a factor of safety as well as a factor of danger for the human dietary. The factor of safety appears in the human capacity for omnivorousness, that is, consumption of a great variety of foods. The dislike for an actual revulsion to a monotonous diet is a drive towards variety, if not omnivorousness in foods. There is no doubt that this tendency or habit of omnivorousness will in part explain the dietary success of our forbears, and of the wild animals, in the absence of specific understanding of food requirements. On the other hand, there is danger in combining the products of human ingenuity in the matter of food processing and food preparation with the capacity to develop liking for foods that are so defective in essential elements that when they are made a preponderant part of our diet, we may develop serious malnutrition. Three of such common foods today are the refined sugars, polished rice, and bread made out of our modern patent flour. These are good foods. We can, and we have developed appetite for them, but because of refinement, they are so defective in many essential dietary elements, that they can lead, in fact they have led, to nutritional disaster when they make up too large an element in our over-all food consumption. I think it is particularly important to recognize the safety in dietary omnivorousness, to recognize the fact that we can and should develop liking for, that is appetite for, a great variety of foods as soon as feeding at the breast or by bottle is supplemented by the common foods of man, because these likings or appetite are probably most easily established in the early years of life.

When good food is abundant the gray squirrel eats the germ in the grain of corn and discards the rest. We eat the rest and discard the germ. The pregnant and lactating squirrel (a herbiver) eats bones when she can get them. So do cattle (another herbiver) ranging on land poor in lime.

think in terms of malnutrition. This comes in only in the case of those people who indulge in alcohol to excess and so constantly that consumption of food for adequate health is impaired, presumably by impairment of brain function, although action of chronic alcoholism in this direction on the alimentary canal and other organs of the body cannot be excluded. Obviously the cure of this form of malnutrition lies neither in supplying more or better food or more cash for the latter would be likely spent for more alcohol. This malnutrition is obviously secondary to chronic alcoholism and this in turn may stem from hereditary as well as social forces that so far as we know today do not spring from any form of malnutrition.

(J) *Myopic Federal and State laws and regulations limiting free production, transportation, and sale of good foods.* A writer has called these federal and state laws and regulations: "state barriers for starvation." I have before me a list of these federal and state penalties on good foods. There is a federal tax of ten cents per pound on colored margarine. This effectively prohibits the sale of this margarine in the United States. The experience in Europe and the United States goes to show that margarine palatable and of a nutritious value, in all probability not inferior to good butter, can be made out of vegetable fats or animal fats other than that in milk. Such margarines can and usually are fortified by the addition of the vitamins present in milk fats. We usually add a non-toxic color to winter butter, without either labeling or taxing it, but when this color is added to margarines our federal government taxes it at ten cents per pound. Ostensibly this law was enacted for the protection of the consumer against deception. That phase can be taken care of by labeling, for most Americans can read. Actually the law was forced on our country by a pressure group, and I fail to see where the law works in the interest of our fellow-citizens in the lowest income group. Were all federal and state restrictions on good margarines swept overboard good margarine could probably be made and sold at half the cost of good butter. It appears that thirty states have themselves absolute prohibition against the sale of colored margarine. I am talking to citizens of Texas. Yesterday our train stopped at Temple, a city "deep in the heart of Texas," long enough for the passengers to find

We do not know when or how these primitive appetites were lost to or suppressed in man.

The vagaries of appetite may lead to malnutrition in two directions. It may lead to eating too little (eneraxia nervosa) or eating too much. The chronic and serious depression of appetite, usually has a psychological basis both in children and in adults, in fact it may follow a period of such great appetite that the person is eating to marked obesity. The criticism and the ridicule of this obesity by the obese person's friends, and associates, may ultimately bring on such a mental state that for weeks, months, and years, the eating of the very best of foods leads to vomiting. Fortunately these cases are not numerous, but obviously the cure here is neither more money, more food or better education as to foods. Perhaps the most serious aspect of the vagaries of appetite as an obstacle on the path towards optimum nutrition is that condition where the pleasures at the table so dominate in the individual's life that eating to the point of obesity follows. To be sure obesity may parallel an incipient malnutrition of factors other than calories in the diet, but I repeat, in the experimental animals, at least, chronic deficiency in any one essential dietary factor impairs or retards both growth and weight. Since obesity is more than twice as prevalent in the American population as is underweight of equal degree, maybe we should give more attention than we have up to date to this aspect of malnutrition because, depending on the degree of obesity, this condition is a strain on the body reserves, renders man less fit for many tasks and shortens his life span.

(I) *Chronic Alcoholism.* As a food alcohol is among the most defective and most expensive. . . . Curiously alcohol in moderation is not infrequently taken before or with the meals with the avowed purpose of easing or adding appetite and digestion. No animal below man seems to need this stimulus, although it is proven that moderate amount of alcohol does increase the secretion of gastric juice whether or not we need that increased amount of gastric juice. It is well known that alcohol, acting both on the alimentary canal and possibly also on the central nervous system may induce temporary nausea, vomitting and anorexia and intolerance for food. This is not a serious aspect when we

lunch. At the Santa Fe Cafe butter was not served with the bread and buns. I called the manager, and he informed me that butter could not be bought in that city. I asked for margarine. The Manager replied, "I cannot buy or serve margarine without paying a state license." If this is so, it is a poser. For the State of Texas produces a great part of the fat (refined cotton seed oils) that go into the good margarines of today. Has statesmanship in national nutrition vanished? Twenty-nine states prohibit the importation of so-called "filled milk." That food is a combination of skimmed milk and animal or vegetable fats other than butter fat. This food, like margarine, can and usually is fortified with the vitamins found in good condensed milk. Northern dairy states discriminate against margarine and "filled milk." Southern states retaliate by restricting dairy food from the northern states. It appears that several states recently have forced higher prices on dairy food by requiring inspection at the source of supply by officials of the importing state, an inspection duplicating that of the producing state. While these laws and regulations, state and federal, are dictated by selfish interests rather than by the dairy welfare of the nation as a whole, they probably do not play a large role in any malnutrition existing in our country in terms of numbers of people, except possibly among the poor. But it should also be said that any remedial measure tending to promote a good diet even for the poorest of our citizens should not be overlooked in our overall program for national nutritional welfare.

(K) *Wishful Thinking or Worse.* Even at the risk of concluding this discussion on "a sour note" I designate the last "obstacle" wishful thinking or worse. We, the laborers in science, must examine our moorings, lest mirages and miracles replace proven reality, and we too become the blind leaders of the blind. I know as yet of no dietary factor automatically assuring even in a man of science the rule of reason every day.

A high ranking Government official in Washington said recently: "Defective stamina, intelligence, judgment, will, stability, can be treated by doses of synthetic vitamins." Since this Administrator is neither a chemist, biologist, nor physician, the information on which this extraordinary assertion is made must have been supplied by some one of our

scientific colleagues, on whom rests the primary responsibility. Treated? Yes. These and other human impairments have had their therapies by the thousands. We all can "call the spirits from the wasty deep." But, do they come when we call them? If treated means treated with proved success, then it seems that a fractional potential has been turned into a universal affirmative. A cautious working hypothesis, such as the following: "Deficient diets, short of producing a full blown deficiency disease may be responsible for such vague symptoms as mental depression, indigestion, easy fatigue, loss of weight, retarded learning ability, and impaired vision," is termed a proven fact, without further evidence. The Administrator supports his statement with the following tale: "Recently I was told that a western trucking company had actually achieved a reduction of its night accident rate by providing all its drivers with bags of raw carrots at the beginning of each trip." We are not told what the truck drivers did with these bags of carrots. Did they hang them around their necks, or did they chew and swallow them? Or was this little item not checked? If they chewed the carrots, somebody who knows should have told those concerned that chewing carrots or chewing the rag are aids to keeping awake, no matter what either may do for the rhecopsin (?) of the retina in the way of better vision in faint light. I know of no statistics showing what factor drowsiness, apart from poor vision (night blindness), plays in the safe operation of trucks at night. Some years ago a New York physician reported improvement in the scholastic record of New York City's backward children by feeding them extracts of the pineal gland. That "promising" therapy seems to have passed on. Now, vitamin pills perform these miracles, apparently even when heredity has been niggardly, and accidents and disease have left their marks on the unfortunate individual.

We are told by a colleague in chemistry: "It is recognized already that one vitamin can and does cure mental derangements." This is stated without qualifications, while as a matter of fact mental derangements are due to a great diversity of factors, including heredity, mechanical and chemical trauma, and cerebral ischemia. The value of the vitamin B complex in mental derangements seems to be largely limited to those accompanying advanced pellagra and

chronic alcoholism. The 1942 faith and hope in universal health miracles from synthetic vitamin pills seems premature, if not immature. When I see our institutions for the feeble minded and the insane, and the criminal evacuated and closed by giving any or all of our 1942 variety of vitamin pills to these unfortunate fellow citizens, I, too, will sing "Hosanna to the Highest." This scientist goes on to say: "Good diets, which mean an abundant supply of vitamins, promote intellectual keenness. . . . There can be no doubt that much dullness on the part of school children . . . can be traced in part to lack of the proper kind of food and especially lack of enough vitamins." These are broad and important generalizations. But I know of no evidence that an ample ingestion of vitamin pills will materially improve the scholastic record of the millions of children and young adults in our schools. These assertions are just too good to be true. Human biology is not that simple. Another colleague in chemistry tells us that the Germans "have enjoyed a more generous supply of thiamin and other vitamins which grains provide than have Scandinavia, the Low Countries, France, Spain, Italy, or the British Isles." Perhaps pacifism is a problem of malnutrition. Yes, the god "Mars" is traditionally pictured as a well-nourished specimen, and if good nutrition leads to war, and malnutrition to the striving for peace, what kind of diet has enabled man to discover the scientific method, to develop a sense of justice, a spirit of fair play, a love, respect, and preference for truth and individual honesty? Are modern science and modern education sequellae of malnutrition?

Recently a subcommittee on Medical Nutrition of the National Research Council presented a report on malnutrition, under the heading "Recognition of Early Nutritional Failure" and with two tables of signs and symptoms. I fully agree with this Committee when it says: ". . . there is imperative need for (a) determination of the actual incidence of early deficiencies among the general population and for (b) the establishment of satisfactory diagnostic criteria for the recognition of such conditions." But after tabulating no less than 29 alleged signs and symptoms of early or incipient dietary dificiencies *that even laymen might observe and diagnose*, the Committee seems to wipe out its entire tabulation and report by this statement: "*Implicit in the difini-*

tion of the problem and in the foregoing statements is the fact that no symptoms or physical signs can be accepted as diagnostic of early nutritional failure. Certain symptoms and physical signs, however, when verified by a competent physician and when other possible causes have been ruled out, should be considered as significant indications. If this latter statement is true, and I subscribe to it, their tabulation is misleading, if not false in toto, insofar as present known facts of incipient dietary dificiencies are concerned.

The Committee lists lack of appetite as a sign of incipient malnutrition. This is contrary to my experience, both in man and in animals. I saw hundreds of thousands of undernourished people on the continent of Europe for the Winter of 1919, but, unless moribund, these people were eager for good foods. They ate the most unappetizing foods. At the end of over 40 days of complete starvation a person, otherwise normal, has an appetite for food keener than at the start of the fast. I have had dogs for various research purposes, fast much longer than 40 days. At the end, or towards the end of these long fasts, these dogs grab food eagerly. To be sure, the rat on a diet deficient in the vitamin B complex will after a while eat less and less of this ration. But it will, unless moribund, eat a better ration. So appetite is not lacking. But it is clear that appetite for food being seriously impaired by any cause, will ultimately lead to malnutrition.

These alarming claims (100,000,000 Americans do not have a good diet) for national malnutrition in our land appear to be based primarily upon a series of surveys conducted by the Bureau of Home Economics of our Federal Department of Agriculture. These surveys embraced some 4,000 urban and village families of various levels of income and some 2,000 rural families of varying levels of income, selected from representative regions of our country. The surveys consist in reports from these families as to how much money they spent for food, and what kinds of food were bought, and, in the case of rural families, how much and what kind of food they consumed from the crops on their own farms. These field investigators (some of them on WPA) had to take or did take the people's word for all of these alleged facts. It is impossible to determine the degree of accuracy as to memory of whatever member of these families gave the

facts or alleged facts to the enumerators. The precarious character of such data should have been apparent to any scientist who is free to work and think.

On the basis of the kind and quantity of food bought or grown on the farms, the Bureau of Home Economics estimated the diets of these families as excellent, good, fair or poor. No physical or medical examination was made of the members of these families. Not even such a simple physical fact as the determination of the body weights of the people involved seems to have been undertaken. The necessity of such checks should also have been evident. The value of these statistics must largely be left up in the air as regards evidence for good or bad nutrition in our country by neglecting such an obvious factor as medical evidence of the health status of the people concerned, even though examination would have disclosed only advanced malnutrition.

How does Dr. Parran's interpretation of these statistical studies by the U. S. Bureau of House Economics check with data from other sources? Hospital statistics (admission, mortality rate) do not reveal significant national malnutrition in United States, except for pellagra in the South. Of course, the mortality statistics reveal only terminal malnutrition, and hospital admission statistics tell us only of malnutrition recognizable by present tests. Chronic malnutrition shortens the life span, but last year the average length of life of our citizens reached an all time high, or 63.42 years. There is some statistical evidence that our children are growing faster and taller than in the past, that college freshmen are taller than a decade or more ago. Children and youths do not grow faster or taller on inadequate diets. But we admit freely that these statistics do not cover our entire population. They are, however, indicies. Malnutrition on a national scale does not lead to obesity, quite the reverse. This is certainly true of the experimental animal. And that was my observation in the war devastated countries in Europe at the conclusion of World War I. Recent studies by the Life Extension Examiners show that 10 per cent or more overweight is nearly three times more prevalent (28%) in the United States than 10% or more underweight (12.8%). It is a curious coincident that the percentage of obesity in our people should come so close to Dr. Parran's estimate of the people having a good diet (25%). The obese may enjoy

a good diet, but they do not use it wisely. Apart from pellagara, perhaps obesity is the most serious aspect of malnutrition in our country.

If 100,000,000 Americans, in times of peace and food abundance, had poor diets, that should have been revealed on medical examination of our millions of young men for our Army and Navy. All these data are not yet assembled and analyzed, but according to Dr. Rowntree, the first 800,000 men, age 21 to 35, examined in the 1941 U. S. Army draft had an average height of 67.5 inches, or exactly the same average height as our drafted men in World War I. But the 1941 men were on the average 8 pounds heavier than the Army men of 1917-18. We do not know whether these 8 pounds represent muscle, bone or fat. These data on the 1941 draftees do not point towards an overwhelming malnutrition in our country. This should give us some assurance and some happiness. But we should not be content, not rest on the car until we have discovered (a) more adequate test of incipient malnutrition; until we have cleared our land of myopic food practices, seen dawn of understanding dispelling our fog of ignorance as to the nature of health and the nature and role of foods; until we have reached first base, at least in driving pellagra from our homes. We have the knowledge as to both the causes, the prevention and the cure of pellagra. We have the food to do it. And yet we have made scarcely a dent on this national disgrace. No, my fellow citizens, the day of rest and contentment for the students of human health is out of sight in war, and will not be in sight with peace. For this road is long, tortuous, and difficult.

MEDICINE LOOKS FORWARD; THE ROLE OF SPECIALISTS IN MILITARY MEDICINE

E. H. CARY*

The subject assigned me on this occasion is sufficiently broad to satisfy any essayist. There is in it, however, a very definite suggestion that history be disregarded and the essayist be cautious about delving into the past, however interesting was the part played by medicine in previous wars.

We all concede that if there was one outstanding gain following war at any period of history, it seemed to come from the medical man's ability to record his observations and thereby add to the sum total of knowledge which could be used for the benefit of mankind not only in war but in peace.

It has been said that many of the great conquerors were those fortunate in having the food for their army and people, to sustain physical strength and morale. Food would aid in defeating epidemics and the ravages of disease, which so frequently determined who was victor in War. Many a plumed knight lost his chance for high military honors when he and his men were beset with infections and food deficiencies and lacked sound medical help.

In this great country of ours during World War I, there were fewer doctors in the service than have been called in to the present effort. We all know that those who were in the army then were less prepared as a whole to render the tremendously improved medical care which is now available.

May I be permitted to make the observation that the aftermath of the last war did bring to the American People better medical opportunities than we had before. It did so not only from the experiences that the medical man had, but from the awakening in his breast of the desire to improve himself, and out of it there came a great many men who were able to utilize known facts more definitely for the aid of some part of the body. This same man may have been a fairly good general practitioner but he was looking forward to the day when he would know something well, and

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the War was his opportunity. The outcome has led in part to a tremendous number of specialists.

According to the A. M. A. listing, made as of April 1, 1942, 52% of the physicians under 45 years of age are specialists. This includes both part time and full time physicians. In the armed forces, as of October 31, 1942, there were 16,637 specialists, leaving a total of 23,337 specialists under 45 for civilian practice.

I have just said that these 40,000 men devoting their lives more or less to some specialty are under 45 years of age, and this does not account for some 45,000 other specialists, who might be said to be both part time and full time physicians, who are over 45 years of age, and who are a part of the medical life of this country.

The point previously made was that out of the last War men came back home with new ideas and with a different outlook. Many had acquired sufficient experience in some department of the war activity which caused them to seek post graduate training. Many left their homes and located in other cities, and apparently this large group, added to those we had at the time, make up this 45,000 over 45 years old.

Whether it can be said that the devotee of medicine, who was looking forward, created this large group who would be content to master a part of medicine, or because of the individual desire to be of service in a limited field, or because it was felt that the specialist of that period was faring better economically, whatever the urge, specialism became more and more accellerated through our scheme of medical education. From Weiskotten's survey, published in 1932, the statement was made that 70% of the students of medicine at that time would eventually practice medicine in some special field.

He says with some certainty, in 1932, that many of the physicians of that day assumed the responsibility of the specialist who had not acquired an adequate, well-organized and systematic graduate training. It is also true that in spite of the outstanding developments which have occurred in a few institutions, there has been no general recognition as to what should constitute adequate training.

When Weiskotten wrote this paper he had in mind what the A. M. A. was doing toward establishing fundamental principles towards courses leading to the specialities and he assumed that a period of training would range from two to four or more years. He stated there should be adequate provisions at all times that there should be at least 8 to 10 thousand graduates in training for the specialties.

Does medicine look forward to a continuation of this urge? I do not see any evidence of change, but I feel reassured about one thing. The 16,637 specialists in the armed forces as of October 31, 1942 (more to be added to this number), are sufficiently numerous in the army to divert many from their special field into a broader field of medicine and if the war should last long enough there could easily follow a changed attitude on the part of the profession. This could affect that vast number of men who are still young and adaptable and in all probability would be made better able to meet the necessities of the practice of medicine whereever they may be.

Again adverting to the experiences of the last War, how much blame should be attached to medical lack of initiative, in not foreseeing the combination of conditions which led to the world-wide catastrophe of the malignant form of influenza, which invaded this country, whose citizens were well-fed and apparently capable of resisting the ordinary ravages of disease.

Surely the vast number of diseases, such as typhus, which followed in the wake of war in Serbia and Russia, could not be charged wholly to the doctors' lack of interest. Was it possible, however, that somewhere along the line the medical profession failed to point out the horrors of War in the light of pestilence which would follow faulty nutrition and exposures to vermin and many of the viruses et cetera, made widespread through carriers in all crowded situations and the like.

How much have the doctors done to make all of the people conscious of what War means and what follows in the wake of War? Bullets and shell, poisonous gases and bombs take their toll, but disease, and I mean preventable disease, in most instances destroy thousands while the mechanism of war takes few in comparison.

Will our experience of 25 years ago cause all medical men to support our ideals in their individual task and forget their individual problems? Recognizing our responsibility, we may aid in promptly and efficiently checking bacterial invasion throughout the world, the invisible fire which smolders for a good while at one spot and then slowly spreads. Finally, if not choked, it becomes a conflagration which scorches the people to the earth.

Looking forward! What a wonderful thing it would be if we could trust each other as medical men and what a marvelous thing it would be if we could trust those who govern us so that a great profession could join hands with the State in rendering the highest service at its command, feeling consecrated in its work, and when this contribution is made (and it will be made), it will not disturb the medical man in his own ideals and in the evolutionary processes of his development in the practice of medicine. That the doctor will know that nothing is going to happen to him while he is gone, that the unexpected will not happen to him from pressure groups while he is away or when he comes home.

Could you look forward to more helpful humanitarianism than this disposition of a man's talents, freely contributing his hard-earned efficiency through long years of study and triumph over difficulties. Pray God he could but know that his service to Public Health would be properly appreciated and that some of his conferees in high places would not sell him down the river.

Where would Public Health be if there was not always the co-operation of the medical practitioner, and how great would be the future of the Public Health endeavor if in conjunction with those who serve the State, every doctor was utilized to the limit as a Public Health Agent. Not through appointment, not through monetary influence but through the co-operation of the medical practitioner throughout the land, such as Vaughn brought into service in Detroit some years ago. Every forward looking, properly educated doctor yearns for the day when people will be well and he wishes to play his part through contact with the patient and direction to keep him well.

The distinguished Dean, who has preceded me, gave an interesting address in 1941 in Chicago. He made the point in his address of emphasizing: "An appropriate and significant special opportunity in general medical practice, is preventive medicine, handled on the basis of health advisers on a retainer fee." Many County Society programs tend in this direction.

It is conceivable that an ever increasing number of diseases that used to occupy the time of physicians will be eliminated if the patient were seen earlier and often.

One of my distinguished friends from Minneasota recently pointed out the lack of material for clinical teaching in tuberculosis and syphilis in Minnesota. For over 25 years they have been as careful with human beings in diagnosis and prevention as we have all been with animals. They have used tests and x-ray study to find out if patients required institutional care and so tuberculosis has finally reached a very low incidence and so it is with syphilis. We can easily look forward to a time when this question of prevention will cease to be a Public Health question run by the State. It will surely fall where it belongs to intelligent doctors, who will assume the individual responsibilities for the individual patients and Public Health efforts will then be multiplied throughout the profession into the homes of everyone.

Felix J. Underwood, an interesting Public Health officer, suggests that they concentrate upon:

1. Communicable disease control—with especial reference to the venereal diseases.
2. Sanitation—The very elemental phases of health work need more emphasis, particularly ordinary sanitation, safe water and milk supplies, protection of the food supply, sanitary methods of excreta disposal, and drainage.
3. Industrial hygiene—with production of tools equipment being a primary essential to defense, the health of the worker assumes a place of first importance. It must not be neglected.
4. Rehabilitation—Based upon the large number of rejectees we have had, which we feel is a good crossection of the total population, it goes without saying that some action must be begun immediately to boost the physical status of these rejectees where possible.

Well and good, but the latter paragraph suggests the views on rehabilitation were based upon the rigid examination for those who first entered the war, since which time, many of the young men, who were not acceptable, are now being freely taken into the war. In other words, those who could not see perfectly, who had some defect in their teeth, and who had in instances, easily remedied defects are now being taken freely into the war, but unquestionably these early examinations brought about very widespread discussions and those who tend to the left and are every ready to grasp any so-called evidence to further their purposes made it appear that our young men were tremendously handicapped and there must be legislation to remedy such terrible physical deficiencies. All of us who had something to do in some way with the men who entered the last war recognized that there were a vast number of individuals who had similar defects but in addition to these defects many of them were so badly nourished that sending them away from their homes to the army was a blessing because they would get better food, properly prepared, proper exercise and come home better off than when they left.

I was chairman of the Judicial district of my part of the state and we examined over 5,000 young men on appeal and many were sent to the war, knowing that they would be tremendously improved and would come home with better knowledge of food and how it should be cooked and in all probability would bring about a better understanding at their own homes where education was lacking on dietary subjects.

In other words, we have always had the undernourished and we have had those with bad teeth and those who have been born with refractive errors. This latter cannot be prevented, the bad teeth and under-nourished can be, in a measure.

It is our duty as a profession to look forward to the time when these preventable conditions will be removed and a better economic situation, undoubtedly will greatly facilitate this happy event.

But looking forward! We should also as a profession see to it that those who feel apparently that they alone are their brother's keeper, and expect to use the doctor to suit their own purposes, will become more rational and less the

agitator. We all believe in evolution and I do not know of any way of having a permanent reform which disregards the process.

As to the part of the subject which deals with the role of the specialist in military medicine, we should not lose sight of the importance of the Public Health Engineer as a highly trained technician in the Public Health Service.

Public health engineering, as stated by Flemming, has to consider three major questions:

1. What shall be our attitude toward the maintenance and further development of Public Health Departments?
2. How can we best provide the necessary service for the new defense industries?
3. How can we assist in the provision of essential service for the armed forces?

In most public health matters, a line cannot be drawn between civilian population and the military forces. You will recall how, in 1918 and 1919, influenza swept around the world, sparing neither armies nor neutral nations remote from the war zone.

Qualified public health officers can rightfully be called specialists and in the public service you find many different types of specialists, all of whom play an important part in military medicine. This service to be made effective is so varied that it includes the veterinarian who inspects meat, the engineer who plans the sanitation of a camp, bacteriologist and epidemitologists, etc. etc., undoubtedly contribute to the conduct and also prolongation of War.

In November 1941, the Medical Clinics of North America was devoted to military medicine. The numerous articles written by specialists give a very broad explanation of the many subjects treated. You find at the outset that the selective service program utilizes some 25,000 physicians and dentists, who voluntarily give their service and a portion of their time in connection with selective service. While the 6,4000 local boards do not require specialists in the general setup, there is the local medical advisory board made up of specialists and usually handles referred cases from a group of the local boards.

From this point on, the selectee should be able to follow through the necessary routine of any army examination

which would make him acceptable as a common soldier. Those who apply for service as flyers, or submarine service are given a more rigid examination by specialists in the army service who understand the stress and strain of service of this character and the mental and physical factors to which the applicant should be adaptable.

When we consider the many nervous and mental hospitals which have been built to care for the nervous and mental cases among the legionnaires of the last war, you can appreciate the tremendous responsibility of the psychiatrist of the present day, who should have plenty of time to examine every young man entering the service of his country, certainly before the government assumes the responsibility for this present and future nervous reactions. The psychiatric aspect of military medicine as described by Lauren H. Smith is one of the most comprehensive articles one could read, and, as an American citizen and taxpayer, I only hope that the vast number of neurotics who would be unable to stand the pressure of war will be examined by competent phychiatrists and prevented from entering military service.

It may be of some interest to refer to an old chart where the specialists in medical practice radiate around the family physician. Black says of the number of specialists he was able to list, 28 were brought into the literature prior to the first of the nineteenth century, and 114 after that time. There are also a number of moderns who have not yet been accorded a place in literature. These include, for example, thirteen divisions of surgery, numerous breakdown in medicine, practices related to eye, ear, nose and throat specialty, and other making a tremendous effort to become classified as specialists.

Like the Egyptians, we are confronted with a subdivision of the human body, which will create a vast number of new specialists. We are forced to concede, however, there is justification for most of them. For example, the endocringologist, whose work has been based upon numerous clinical and pathological observations, has been given recogtion. It is true this practitioner is unable to explain the function and pathology of many of the glands which come under his specialty. But, knowledge of the glandular system has been greatly increased through the interest of workers who have devoted their lives and efforts for better

comprehension of this particular part of the body in relation to the whole.

Today we can say endocrine gland research, nutrition, physical chemistry, immunology, metabolic psysiology, and psychology are commanding the attention of many brilliant men, who justify the appellation of specialists. No doubt the endocrinologists' role in the present war may be limited but undoubtedly could be used as a consultant.

William Henry Welch, paints a picture of medical men, reaching out to all the other sciences for aid; as traveling in cycles, sometimes to one field of medicine, sometimes to another, but always, in the end, returning to the advice of Hippocrates, to assay the facts in his own clinical field.

One of the interesting phases of this scientific age is the number of older specialists, who did not have the benefit of training in the fundamental sciences. Some of them, in marvelous fashion, have kept faith with themselves and their patients, because they have acquired knowledge as it has been made available. Great is an organization, such as the organization of medicine, which offers to its members who live in a school of experience, the advantages of post-graduate education. We all know that such educational opportunities have been consistently brought to every understanding and ambitious physician. The older specialists, well trained in youth, and ambitious and studious, are the masters. They are the leaders who have brought medical education to this new day, wherein younger men have the advantages of an educational system which requires more of him before he may begin his life work. All of which redounds to the glory of the leaders of the immediate past and present.

Forty years ago the requisites of specialism were well understood, but few physicians voluntarily equipped themselves. Competition within the profession has now become such that a young man would be foolhardy to enter the contest without extensive preparation. Those of us who have been engaged in the educational field throughout this period of medical improvement, realize that high standards for entrance into our medical school and rigid demands of the factulty, do deter, but instead stimulate, the desire of ambitious students to become physicians.

The future yields always to educational influences. We had succeeded in formulating requirements which required years of study and preparation to become a graduate of medicine. We have succeeded in implanting in the young graduate's mind the importance of accepting clinical opportunities in hospitals and study and earning fellowships which required additional years. As intimated before there were so many medical men having had this experience that those who were following in their wake dared not enter the practice of a specialty without preparation which satisfied their colleagues.

It looks now as if the Council on Medical Education had yielded to demands from many places which will definitely lower the standards which required years to create. This War is an excuse for many things but to me there is little to be gained in the cry for numbers when undoubtedly the quality will be lessened when we yield to expediency.

Regarding the role the specialties play in the present War, from a recent letter of Major Harold C. Lueth, I am furnished with this information.

"In the first studies conducted by the Committee on Medical Preparedness, A. M. A. and later taken over by the Procurement and Assignment Service, there were 176,191 physicians in the United States. Of this group 85,964 physicians were in specialty practice and 90,227 physicians in general practice. There were 38,959 physicians under 45 years of age in general practice and 41,978 physicians in specialty practice.

"There are no statistics available as to number of men certified by Boards, however, there are studies concerning this problem under progress."

Major Leuth continues: "The exact number of men in service cannot be released, however, there are about 43% of the physicians called from civil practice to duty with the armed forces in general practice and 57% in specialty practice.

Your fourth question: "Whether due to the fundamental education of these men they have been diversed from their specialty into general service and if so, approximately how many have been so used? is difficult to answer since the exact duties of medical officers with the armed services are not a matter of record with the Procurement and As-

signment Service. There have been repeated assurances from the medical corps of the services that every effort is being made to utilize the services of specially trained men in their field while on active duty."

The Army is made up largely of young men and while in base hospitals specialists can be utilized to a great advantage with those few who will have diseases which require special attention, it would seem that specialists will have to become once again as previously indicated actively interested in practicing general medicine and surgery.

Now while it is true that the men under 45 years of age have been pretty well trained in general medicine and hospital service before becoming specialists, it is undoubtedly of advantage to the soldiers who are sent to Africa and many other places that the modern doctor will be able to discard for a while his interest in special parts of the body and renew his interest in the whole. Undoubtedly this experience will bring about better practitioners when they come home. Many of them will have a better conception of their own field if they should be interested in resuming their special practice.

One of the interesting things in writing a paper of this kind is to look through articles written for special Journals and see how each of these groups has approached the question of their responsibility and future service with their countrymen who are in the various branches of the service.

I can imagine the syphilogist being confronted with many fresh cases and a new opportunity to treat large numbers—utilizing the research work which is now going on and particularly in our own institution by a former student of your university, Dr. Arthur G. Schoch. While the Army has not yet universally adopted the sixty-day method undoubtedly the new work will lead the way to abandonment of the eighteen-month treatment.

To conclude this paper with a more specific reference to the role of specialists in military medicine, there are some of the specialists which we can group as far-advanced during the last war, ophthalmology and otolaryngology among them. Yet it is true that the mechanism of war has materially advanced the occulist and aurist who have had to keep pace with the requirements of aviation. The capability of the prospective flyer has required additional special

knowledge both as to his eyesight and to what happens to his hearing. Barometric pressure variations are entirely different from the modern flyer and it has required experience and careful analysis for both the eye and ear men to keep pace with the necessities of the soldiers who are in this field of endeavor.

Undoubtedly, as previously indicated in this paper, psychiatry, and neurology and neuro-psychiatry or to whatever group these gentlemen belong they have a larger conception of the possibilities of future claims upon the government and are preventing vast numbers from entering the service.

In the field of surgery (which includes orthopedic, plastic and thoracic surgery) there have been many advances. The handling of wounds is completely different from what it formerly was. The sulpha drugs and new methods of approach to abdominal and other wounds as burns has undoubtedly given the surgical specialist a tremendous opportunity to save many who formerly became infected and died. The record in Pearl Harbor of one mortality to 200 injured is not only the result of the sulpha drugs but no doubt the ability to treat shock.

Fortunately before this war, there had been an extensive lot of work done on shock and the use of plasma for this and other conditions. Plasma desiccated from the frozen state is considered by our workers, Drs. Hill and Muirhead, as an ideal type of plasma preparation. They maintain it should be used in hypertonic form (some four times concentrated) to realize maximum advantages. Plasma in different forms is being used both here and abroad.

Undoubtedly the skill of the surgeon is greatly reinforced with the sulpha drugs and plasma preparations.

Undoubtedly the specialists in internal medicine are reinforced in the same way and medicine broken into its different specialties play a tremendous part in the care of the soldiers and will bring back from this war information due to new experiences. In this connection it can be said that the dietitians are better trained than ever before.

One cannot over-emphasize the importance of the roentgenologist as a specialist who can protect the army from incipient tuberculosis and who can, in addition to this, serve in the various capacities greatly needed by the

other specialists in serving the soldiers of our country.

The Army will have better specialists in dentists, bacteriologists and pharmacy.

In closing I would like to pay tribute to the many well-trained specialists who are working and giving their time freely on Research Councils and various and sundry other scientific committees. While this is true and we should regard their work as of prime importance, we should not fail to realize the well-trained young men in the medical schools of today, who have had clinical opportunities of their own in hospitals, should also be brought into the picture, particularly in Washington, for I fear that it is often true that even the wise man with much experience, if not static, frequently has closed his mind to new ideas.

If we are to have War, let us by all means have freedom of thought and freedom of opportunity and recognition of capable brilliancy.

PSYCHIATRY IN WAR

FRANKLIN G. EBAUGH*

President Rainey, Dean Leake, distinguished guests, ladies and gentlemen: It is a pleasing obligation to present the felicitations from the University of Colorado to our sister institution, the University of Texas, on the occasion of its semi-centennial celebration, as well as to Dr. Chauncey Leake, your distinguished Dean and Executive Vice-President.

The Medical Schools of the University of Colorado and the University of Texas have a lot in common, since both were pioneers in the development of psychopathic hospitals as an integral part of the medical center. The University of Colorado Psychopathic Hospital ante-dates the Galveston Psychopathic Hospital only a few years, and each state medical school has pioneered and fostered the development of psychiatry as a fundamental phase in general medical education and practice. I refer in this connection to the fundamental, basic work of your professors of psychiatry, Dr. Titus Harris and Dr. Hamilton Ford, on the medical wards of the Sealy Hospital, where they have demonstrated the practical application and usefulness of psychiatry as a part of general clinical medicine. Their work is a forerunner of what I feel will be one of the leading medical contributions of present military medicine —that is, the development of psychosomatic medicine in which all clinicians will be aware of and appraise complications that develop as physical repercussions of underlying emotional states.

It is also most appropriate on this occasion that you are honoring a new dean, Dr. Chauncey D. Leake, whose scientific attainments and research productions are universally known throughout the land, and whose remarkable personality and qualifications for leadership will point the way to consistent and progressive scientific attainments in medical education.

It also gives me great pleasure on this auspicious occasion to represent the Eighth Service Command where,

* Lt. Col. M. C., Professor of Psychiatry, University of Colorado School of Medicine, Denver. This address was delivered at the Clinical War Session of the Semi-Centennial Graduation Exercises of the University of Texas Medical School, Galveston, December 18, 1942.

after being granted a leave from my university duties, I now serve as Neuropsychiatric Consultant and have an opportunity to apply, test and prove or disprove the validity of many of the present-day trends in medical education, as well as the phase and specialty I represent.

My experiences in military psychiatry have already confirmed my deep conviction that one of the most important phases in all types of illness is the personal component and that we cannot continue to devote most of our energies in terms of the impersonal phases of illness, since it is the essential duty of all clinicians to deal with the person as well as with the manifestations of disease.

Psychiatry in war has many responsibilities, of which I would like to discuss what I consider to be the main ones, under two headings:

1. Psychiatric problems in relation to the selection and induction of men physically and mentally fit for military service.
2. The recognition, prevention, and treatment of personality disorders in soldiers.

Within the next year or so the addition of 3,000,000 to 4,000,000 men to our armed forces is contemplated. This will necessitate a review of the qualifications of twice that number. It is our belief that with our present knowledge we can profit from our past experiences and create a new organization which will make possible more adequate medical and psychiatric evaluations of these men. This has been very difficult:

1. Because of inadequate provisions for the gathering of information prior to examination;
2. Because all examinations have to be conducted at relatively few induction stations which are, therefore, the narrow point in the funel through which the stream of manpower must flow at greatest speed;
3. Because it makes it impossible to use civilian resources of physicians, psychologists and social workers, and makes it necessary to use largely those physicians and psychologists who are already in the armed services and who are needed with the troops.

In plans for adequate screening and rejection, the purpose would be to develop, test, and apply special methods (1) for the rapid compilation of social histories, (2) for

the rapid compilation of medical histories, and (3) for rapid group and individual screening.

It should be mandatory to secure the cooperation of appropriate agencies in each state in setting up coordinated and unified record systems, which will make available the data which is essential for the compilation of a social history on all potential soldiers. This entails the development of:

1. Methods of identification of individuals (standardized card files, universal registration, universal fingerprinting.)
2. Master files in each state for police records, social service exchanges, all mental hospitals (including private hospitals and those for alcoholics and addicts), all general hospitals, home for the mentally retarded, special classes for the retarded, a central registry for private psychiatric patients and for patients with incapacitating but obscure organic conditions.

We should instigate test screening methods applicable to large groups of men simultaneously, which could pick out of the mass those physiological and psychological deviations which either warrant immediate rejection or indicate the need for further individual examination:

1. By watching the future course of individuals who have been subjected to and scored in such tests;
2. By applying the tests to groups of individuals who have already done well in the armed services;
3. By applying the tests to groups of individuals who have already done poorly in the armed services.

The present method of processing men in our induction stations at best presents many difficulties. These difficulties are natural on the basis of the large number of men examined, the rapidity of examinations, and the absence of satisfactory preliminary data or information obtained from social and medical histories. Then again, psychiatry has its specal problems, since this phase of medicine means a study of an individual's life history, which is the best guide to his personality functioning. It is, therefore, extremely difficult, if not impossible, to make adequate psychiatric studies in induction examining stations without a minimum social history. It would be of the ut-

most aid to the examining psychiatrist if information concerning the school record of each registrant, data or abstracts from hispital records and court records, if any, were available. Likewise, statements from employers on questionable cases, as well as a complete social service record, would be very helpful. This would enable the psychiatrist to work more satisfactorily and accurately. Moreover, this information would supplement the inadequate data now obtainable from Selective Service Form 221.

Available sources of information are now possible through the social service exchange located in many of the larger cities (Dallas, Houston, Fort Worth, etc.). Inquiries regarding state hospital admissions, as well as court records and sentences, can be checked through the proper sources. The requisites constitute an irreducible minimum of data for more adequate psychatric screening.

Furthermore, experiences to date present both negative and positive aspects which should be analyzed in order to develop better methods for the elimination of the mentally unfit from our armed forces. For instance, the experience of the Boston induction station indicates that a reasonable, comprehensive psychiatric examination can be conducted and controlled, with the result of a great decrease in C.D.D.'s from that area later. Here it was found that not more than ten cases could be examined by one man in one hour, and that a trained psychiatrist could not do effective work in examining more than fifty cases in a five-hour day.

Experiences in this service command, as well as a research study for National Research Council, indicate that in our patients C.D.D.'d from service there are usually fifteen possible specific attributes in the past history of the patient which warn of mental unfitness. These are:

(1) Bed-wetting beyond four years of age.
(2) Thumbsucking or nail-biting beyond six years of age.
(3) Failure to engage in competitive games involving risk of injury.
(4) Tantrums in childhood.
(5) Abnormal shyness or sensitiveness.
(6) Preference of playing alone.

(7) Repeated grades, difficulty with teachers, chronic truancy in school record.
(8) Abnormal fears, such as of lightning, dark, bogie man.
(9) Shunning of girls after puberty.
(10) Faints.
(11) Excessive autonomic system reactions to emotion; tremor, abnormal sweating, tachycardia, etc.
(12) Sulkiness under discipline.
(13) Abnormal attachment to mother after puberty.
(14) Stammering.
(15) Obsessional traits.

The negative phases in the problem likewise point the way to a solution for more adequate neuropsychiatric selection and rejection methods. For instance, until comparatively recently several induction stations operated without the services of a trained psychiatrist. Examinations were frequently made on the basis of two minutes (or even less) spent with each registrant. There were very rarely rechecks. At the present time, the rejection rates in one of the largest induction centers in this service command show very few cases of schizophrenia and an amazingly small number of psychoneurotic rejections. There should be a flexible procedure worked out in each induction station whereby all selectees can be graded into several groups, such as:

First group—excellent, good, or average material;
Second group—questionable material, which should always be reexamined and rechecked by at least two psychiatrists;
Third group—obvious rejects.

Guides in the form of questions can be used routinely, but they present a serious danger if they are followed too closely and not used simply to establish leads which will give insight into the patient's behavior and personality makeup. It is extremely important that the examiner utilize to the fullest extent direct observation methods: the approach of a patient to the interview room; the face of the registrant; pupillary restlessness; tremors; excessive perspiration; speech; general attitude, demeanor, and posture. Careful correlation with the objective findings of the other examiners should be made.

It is also important that a brief neurological examination of a patient be made: noting of pupillary responses, examination of reflexes, tests for coordination, etc.

The examiner should follow carefully the regulations established in the official manual. An attempt should be made to classify each rejected registrant into one of the following eight categories:

(1) Mental defect or deficiency;
(2) Psychopathic personalities;
(3) Major abnormalities of mood;
(4) Psychoneurotic disorders;
(5) Prepsychotic and postpsychotic personalities and schizophrenic disorders;
(6) Chronic inebrity;
(7) Syphilis of the central nervous system;
(8) Any existent disease of the brain, spinal cord or peripheral nerves.

Determination of the fact that the inductee belongs in the first category will be the function of the psychologist stationed in each induction center. The psychiatrist should always be consulted in doubtful cases.

The following common signs and symptoms suggestive of personality disorders should prove of help to each psychiatric examiner:

(1) Intellectual inadequacy:
Excessive slowness or inability to learn or obey commands.

(2) Psychoneuroses:
Anxiety states such as:
Panics, attacks of palpitations, pre-cordial pain, feeling of tightness, breathlessness, weakness, cold sweats, dizziness, fainting.
Hysterical reactions such as:
Motor disorders shown in weakness, tremors, paralyses, contractures; sensory disorders shown in various forms of sensory change from anesthesia to hyperesthesia; mental phenomena shown in the hysterical convulsion, amnesia, fugues, etc.
Obsessive states such as morbid and insistent doubts; various phobias, including fear of dirt,

disease, etc.; peculiar repetitious acts, head-turning, checking and rechecking work, and various compelling rituals of thought and action.

(3) Constitutional Psychopathic Conditions:

Atypical emotional reactions such as:

Excitability, emotional instability, fearfulness, evidence of difficulty in getting along with the other men or superiors—such as:

Impulsiveness, querulousness, callousness, being inclined to cultivate insubordination, non-dependability, etc.

Other atypical behavior, such as excessive alcoholism, drug addiction, "guard house lawyer" activities, etc.

(4) Organic Psychoses—i. e., caused by disorders of or injury to the brain:

Decline in efficiency and performance of manual skills associated with which are noted frequently tremors of the hands and face, speech disturbances, decrease in neatness and cleanliness, disinterest, and apathy.

Loss of mental efficiency as shown by: Forgetfulness, defective planning and judgment, emotional instability and explosive outbursts, excessive vulgarity, extravagant ideas, disturbed social behavior, periods of confusion and convulsions.

Physical symptoms and signs, such as headache, digestive upsets, pains, unsteadiness of gait, tremor, paralyses, weakness, irregular and unequal pupils, etc.

(5) Depressive Psychoses:

Loss of spontaneity as indicated by general slowing of activity, decline in interest, loss of sociability.

Depressive appearance.

Depressive outlook as manifested in pessimism, self-depreciation.

Tense and restless activity.

Physical signs and symptoms, such as weight loss, poor appetite, constipation, poor sleep.

(6) Manic Psychoses:
Elation
Extravagant ideas
Braggadocio
Anger reactions when crossed
Negligence
Distractibility
Decreased efficiency
Excitement
} On account of lack of inhibitions and critical ability and irritability.

(7) Schizophrenia or Dementia Praecox:
Seclusiveness.
Loss of normal interests.
Odd and incongruous acts and utterances.
Hallucinations (seeing imaginary things, hearing voices, etc.).
Delusions.
Posturing, becoming immobile, rigid and stuporous.

(8) Paranoid and Paranoic Reactions and Psychoses:
Set ideas regarding the training, preparation of food, dress, rules, etc.
Feelings of being unfairly treated.
Seeing some personal reference in neutral events.
Ideas and delusions of persecution—i. e., the person having ideas that others talk about, laugh at, or are injuring and poisoning him.

(9) Toxic—Infectious Psychoses or Delirious Reaction:
Difficulty in grasp leading to confusion and disorientation.
Poor retention and recent memory.
Feeling of apprehension and fear.
Hypersensitivity to sounds.
Hallucinations—i. e., seeing, feeling, hearing imaginary things.
Delusions of being injured, killed, etc.
Physical signs of the existence of some:
Toxic agent such as alcohol, drugs or poisons.
Infectious states.
Exhaustion and fatigue.
Food deprivation.

Registrants showing the above difficulties should be brought to the attention of the chief surgeon of each induction station and rejected.

To summarize: the present neuropsychiatric examinations in our induction stations are not entirely satisfactory. Since psychiatry is that phase of medicine which deals with the pathology and therapy of the person, there are essential difficulties in establishing an adequate examination, in contrast to the routine examination of organs and systems. The personality functions of any individual, as shown in his behavior, cannot be understood unless there is an adequate record of his past performance. It is, therefore, essential that a social and medical history be obtained on each registrant before examination and made available during the examination.

The data now being analyzed on the large number of C.D.D.'s in this service command, as well as the common factors found in individuals who develop psychiatric difficulties after induction, are clearcut and decisive and indicate conclusively the importance of utilizing available sources of information such as school records, hospital records, court records, and vocational records.

Experience likewise has shown that it is not possible to make a minimum psychiatric examination on more than fifty registrants per day, or ten per hour, for each examiner. There shoud be individual and private rooms available for the neuropsychiatric examinations. Each induction station should utilize to the fullest extent flexible work sheets, classification procedures, and rechecking examination procedures which seem best to the medical personnel.

Although the situation pertaining to present psychiatric filtering in our induction stations is inadequate, much good work is now being done. With continued cooperation and collaboration between Selective Service officials and the Army induction officials, much of the present waste in money, effort, time, and man-power will be eliminated.

The second phase of my paper deals with the importance of adequate recognition, prevention, and treatment of personality disorders in soldiers. After induction into the Army, the soldier's service may arbitrarily be divided into five periods:

1. *The preliminary period of training,* that is, the period immediately following induction into service during which the recruit is taught Army discipline and regimentation, is acquainted with the basic responsibilities of a soldier to himself and his unit, and meets new friends.
2. *The indoctrination period,* during which the soldier is instructed in the refinements of self-protection, warfare, and special or technical duties and tactics. In a peacetime Army the soldier finishes his enlistment or active service at this stage.
3. In time of war, the second period passes into *the pre-engagement period;* that is, from the time the soldier realizes preparations are being made for moving into the combat zone until active engagement occurs.
4. *The period of combat.*
5. *The demobilization and social readjustment period.*

Evidences of personality difficulties in the soldier and officer are apt to appear, in order of frequency, during the first, early part of the second, and in the third and fourth periods.

In general the prevention of personality disorders and, therefore, of many administrative problems and future disability claims based on psychiatric illness can be decreased to a considerable extent by:

1. The close cooperation of company officers and medical officers in watching and interpreting the behavior of the men so that adequate psychiatric diagnois and treatment can be instituted as soon as possible.
2. The elimination from the service within a short period of time after induction of all recruits and selectees with manifest psychoneuroses, psychoses, and other behavior disorders not conducive to adequate adjustment and efficient performance.
3. The development of *esprit de corps,* or morale, in the men.
4. Sufficient training to insure fitness and self-confidence in the men.
5. Allowing the men frequent rests and distractions from duty.

6. Eliminating from discussions before patients such terminology as "disordered action of the heart" (D. A. H.), "soldier's heart," "effort syndrome," "nervous and mental disease," "shell shock," etc., or any psychiatric diagnosis that tends to designate or implicate a part, or an organ of the body.
7. Recommending that men and officers with incipient symptoms of emotional disorders be promptly relieved from active duty for rest, recreation, and necessary treatment.
8. All possible avoidance of monotony.
9. The promotion of physical comfort whenever practicable.
10. The promotion of sanitation.
11. Evacuation of casualties to convalescent hospitals whenever indicated.
12. Treatment of the psychiatric casualty as near as possible to the site of the inception of the disability.

Psychiatry in war, therefore, has established careful plans regarding the selection and induction and maintenance of mental health after induction. Although the plans are well established, much remains to be done in the effective application of proven psychiatric principles. We should realize that approximately one billion dollars is now being expended in our twenty-seven Veterans' Bureau hospitals, with a capacity of 33,000 patients who are veterans of our first world war; and that 60 per cent of all ex-members of our military service requiring hospitalization are admitted for neuropsychiatric disabilities alone. It is, therefore, of extreme importance that we continue our studies regarding proper selection based on complete social histories and adequate examinations in all cases; and likewise, that we establish careful preventive psychiatric work in the reception centers, the replacement training centers, and the training areas, as well as in the zones of combat.

OBSERVATIONS ON APPLICATIONS OF PSYCHIATRY IN WAR

EMILIO MIRA*

"1. Some misfit civilians do well in army life. Some well adjusted civilians break down under the strain of warfare. But in a high percentage of the cases, well-adjusted civilians make the best soldiers.

2. A shell-shocked soldier if treated as though he were an invalid will soon become one. A soldier with a war neurosis such as loss of speech or paralysis of the arms, if sent back to the security of the base hospital, may become fixed in his protective reaction. For this reason, psychiatric treatment in the Loyalist army in Spain was generally given near the front line fighting, except in the more serious cases.

3. Treatment of shell shock and war neuroses includes both explanation and physical therapy. The soldier is told why subconsciously he develops simulated incapacities; and then he is induced to exercise, work, or do anything that will keep him in motion. Gradually he gains confidence, responds to rest, exercise and good food, and is again ready for service. If a neurotic does not have such treatment but is allowed to stay in the hospital four or five days, his reaction becomes more fixed and is more difficult to cure.

4. Alcohol is a menace in the army. The Loyalist forces constantly carried on a propaganda campaign against excessive use of alcohol. Psychiatrically, the heavy drinker is a weak personality. A highly coordinated person cannot stand excessive drinking.

5. Morale in war time is not mysterious—it can be explained as a condition of individual and group mental health. Morale is high only if a nation knows definitely what it is fighting for.

6. Both fear and hatred undermine morale. Fighting for a cause and being devoted above all else to what one is fighting for is the greatest single factor in morale. The Spanish Loyalists become absolutely fearless as they

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* Informal notes on the Salmon Lecture, given under the auspices of the Hogg Foundation at the University of Texas Medical School, November 21, 1942, by Emilio Mira, M.D., Professor of Psychiatry, University of Buenos Aires, formerly of Barcelona.

fought the Germans and Italians. In Madrid, instead of running from the exploding shells, the citizens would watch from the rooftops and gamble when they saw the flash of the guns as to what size of shell was coming over next.

7. Physical exhaustion undermines morale. German officers know exactly when their men must be relieved from active fighting and given rest. They also know the value of good food. Civilians in Europe will starve to death this winter before any German soldier will go hungry.

8. Warfare itself is partly psychological. Principles of sound, rhythm, and sight are being used more in this war than ever before. The German artillery will fire at the rate of ten rounds a minute and then suddenly step up the tempo to one hundred rounds a minute. Suddenly there will be no firing, and then it will start without warning at a different tempo. This change in pace is supposed to unnerve the enemy. The German army has also used sound devices with its high explosive bombs and sirens on its low-strafing airplanes.

9. Fifth columnist work also involves psychological principles. Germans have infiltrated in South America for generations. Instead of holding themselves aloof from the native population, they intermarried, settled in the smaller cities, and became prominent leaders in business. Many of these people have been trained in fifth columnist work and are ready to act when the time comes. In some way the United States must counteract this German influence by meeting South Americans on their own terms, and doing away with attitudes of exclusiveness and superiority. The German influence is particularly strong in Argentina but even here the United States can win the people if the right attitude and methods are used."

II.

ADDRESSED TO SOLDIERS BUT ALSO OF VALUE TO CIVILIANS

As a soldier of the army ready to shed your blood and give your life for ideals and spiritual values; as comrade whose work and effort will form a better, more generous and freer world, listen:

Pause a moment in this battle to hear in these few pages the well-intentioned voices of those, who, unable to fight beside you with a gun, are trying to help you

to victory by some advice stemming from their own scientfic experiences and observations. Some of these are eternal maxims which can serve you not only today, but tomorrow and always as a guide for the attainment of your desires. For your own sake and that of all of us, do not forget them!

MAN'S GREATEST HERITAGE IS A HEALTHY SPIRIT

Of what use is a healthy body and all imaginable wealth, if the owner because of a weak, unhealthy and deformed mind cannot enjoy them, and is incapable of using them for anything but the lowest animal desires? Of what use are dreams of beautiful horizons if the courage or will to conquer them does not exist? Only a healthy mind has sufficient strength to orient itself and fulfill its destiny in life. Spiritual health manifests itself directly by serenity and steadiness of purpose in face of the future; and by an attitude of loyalty, understanding, and warm affection toward one's fellowmen.

In exactly the same manner that we follow rules of physical hygiene to attain and maintain physical health, just so must we follow rules of mental health to secure spiritual health.

The most simple machine, no matter how strong or well constructed, can be ruined if it is not correctly used and treated. Similarly the human spirit can become unbalanced and exhausted if the rules of mental hygiene are not observed, for only this will preserve it from the disastrous effects of mental conflicts, dislikes and remorse. Grief, disappointment, resentment, or a deeply repressed passion may affect an individual's life more severely than pneumonia or typhoid fever, and may urge the victim to suicide and madness.

The *first rule* to be observed at the battle front is to isolate and denounce those, who, due either to their natural pessimism or intentional ill feeling towards their country, spread depressing or disagreeable news, thus aiding a defeatist campaign. Alarming news, whether true or false, spreads throughout the fighting front faster than any infection, and may lead to a precipitous drop or collapse in fighting morale. Those who defy death are under much emotional tension. This increases suggestibility and ready belief in any cunning or false formula offering escape. "I

must save my life to use it for the sake of my ideals," thinks the soldier, or he may try to persuade himself that "my individual sacrifice will be useless since I, alone, cannot avoid defeat," etc. The underlying mechanism for this way of thinking is the subconscious instinct of self-preservation which suggests "run away." To this the soldier's conscience replies: "I ought to remain at my post." Then imagination, intermixed with fear suggest further: "The others are beginning to run" and then conscience, overwhelmed, but seeking some justification for its abandonment, states while the soldier is fleeing: "It would be crazy to stay and resist if my companions are leaving me." This latter statement is, of course, absolutely false, for in spite of the flight of the others, one's life is always better defended by facing the enemy than presenting the back to him (statistics show that deaths are five times greater in flight than in defense.) Moreover, fleeing *never serves as a useful sacrifice,* not even having the golden value of setting an example. A thousand instances could be mentioned in which the visible sacrifice of one man has completely changed the course of a military action. That is why the defeatist soldier is more dangerous than bullets. That is why he must not only be avoided as if he had the plague, but must also be denounced to your comrades.

The *second essential rule* for the soldier's mental hygiene is to make him feel strongly attached in every way to the military group of which he is a part, and to fulfill all orders and duties, given him by his comrades in command, as if they were his own. From the moment of his incorporation into an army corps, the soldier must realize that individual initiative, disobedience, and lack of discipline leads to a dangerous decrease in the efficiency of the collective forces whose purpose is to protect him. In addition, it exposes him to punishment since it is a moral fault, and consequently he will suffer sooner or later the unpleasant effects of the loss of his own dignity. A soldier who disobeys or neglects an order is as bad as one who deserts from the fighting line. By thus alienating the friendship and respect of his group, he may die like an amputated finger.

Further important advice. If you want to fulfill your responsibilities and duties, remember that you are fight-

ing not only for a political regime or social improvements, but also for the future of all humanity. On your defeat or victory depends a new world based on Justice, Liberty, and Love, from which will arise a new joy in living, which will reach all and to the same degree. You are, therefore, more than a giant. You are a little creator, for from your hands will emerge a part of the pattern of the New World. Be aware of the importance of your effort. Concentrate on it and consciously use all your energy. Do not fight to live! Live in order to fight!

In a short time, thanks to you and your comrades, predatory wars of invasion will be a thing of the past, and the citizens of this new world will seal a fraternal agreement, securing Peace on Earth forever for all men. For this reason it is necessary to direct all your courage to the battle. The more you long for a quiet and happy life, the more vigorously must you fight for early victory. Every hour that the war is prolonged causes new victims among your people. Save them with your will and energy in fighting. To do this you cannot squander your life in sexual excitement, all night parties or drinking. *You must rest as much as you can during your leisure hours.*

If you feel exhausted, depressed, or doubtful, if you envy your comrades because they seem to suffer less or weather the difficulties of the campaign better, remember that a *man's duty has been to compare himself not with others, but with himself!* To become each day a more dignified person, to fight against your own selfish instincts, to overcome your fear, to feel free, and to be better today than yesterday, this is *your Duty.* In direct proportion to the accomplishment of this duty, you will feel happy, even among the greatest calamities.

When you cannot control your emotions or passions, when your brain cannot solve your conflicts, when you feel incapable of recovering your self-control, go without hesitation to see your comrade, the physician, and explain your troubles to him. He will help you, and treat you mentally and physically, and if he thinks it necessary will send you to a specialist. Have no shame in confessing your nightmares, show him the background of your thoughts as you would show him a pimple. Remember that his professional honor demands that he keep your confidences secret.

Above all, do not look for the courage that you lack in drinking or in excess of other poisons (coffee, tobacco, etc.). If you do so, you will accelerate your spiritual decline rather than prevent it.

Now read and meditate on the following, brief catechism: You will find enough in it to stimulate you to attain your maximum goal—"Nothing less than a complete man"—i. e., a reasonable, free, serene, fair, magnanimous, and fertile human being.

Better to die standing, than live on your knees.

Your worst enemy is yourself. Observe and analyze yourself.

Never justify your own behavior on the basis of someone else's approval. Always appeal to your own moral judgment.

Remember that those who shout more, usually feel more unsafe.

Tell me of what you are boasting, and I will tell you what you are lacking.

The supreme good is justified satisfaction of one's self.

Do not judge the action of other people until you know completely all their reasons.

A man's value is measured by the number of persons he is able to understand and respect.

Do not trust to others what you can do.

Do not try to command if you have not learned how to obey.

Do not live in the past. Face the future, for man is what he becomes.

To triumph is good, but to forgive is better.

A good book is worth more than a bad companion.

Protect the weak, and honor all sincere opinions. Oppose without mercy lies and hypocrisy, even though they seem to praise you.

Try to make each of your actions a model of universal behavior.

Follow the slogan: One for all, rather than all for one.

STUDIES ON HYPERTENSION
I. THE EFFECT ON THE RENAL FUNCTION OF DECREASING THE BLOOD PRESSURE OF PATIENTS WITH HYPERTENSION

RAYMOND GREGORY, E. L. LINDLEY AND HARRY LEVINE*

Therapeutic procedures are frequently directed at lowering the blood pressure of patients with hypertension. This raises the question concerning the possibility of harm which might result from the fall in blood pressure. The relationship of the blood pressure acting as the hydrostatic force filtering a protein-free plasma through the glomeruli to the production of urine is well established (1). It seems, therefore, that a significant decrease in the blood pressure of hypertensive patients would decrease their renal function. The undesirability of impairing the renal function of hypertensive patients is obvious.

This problem has been studied by others. The blood pressure has been decreased in the other studies, however, by drugs (2) which are circulating in the blood or by various surgical procedures (3). The results obtained by the former method may be questioned on the grounds that drugs may directly influence the renal function by their local effects on the glomeruli or tubules. Inasmuch as lowering the blood pressure by splanchnectomy, anterior root section, renal denervation and spinal anesthesia have much in common, it is surprising that our results obtained by the last mentioned method are at such variance with those obtained by the surgical procedures.

Our studies of this problem on hypertensive patients have been accomplished by decreasing the blood pressure by the use of a spinal anesthetic, a method not used heretofore for this purpose so far as we know.

METHODS.

Spinal anesthesia with procaine hydrochloride was selected to lower the blood pressure because of its method of action. The effect on the blood pressure is due to the functional interruption of vasomotor fibers as they leave the spinal cord in the anterior roots. Furthermore, there

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is little or no procaine in the peripheral circulation when given subarachnoidally. Bullock and McDonald (4) were unable to detect procaine in the blood of two patients during spinal anesthesia produced by 300 milligrams of procaine hydrochloride. Their method was capable of showing the drug in blood in as small a concentration as 0.002 per cent. In no instance was more than 150 milligrams of procaine hydrochloride employed in our studies. Procaine has no important direct peripheral effect on capillaries or arterioles in the very small concentration in which it may be present in the blood following subarachnoid injection.

The urea clearance of Van Slyke (5) was used as the test of renal function. This was performed by accurately collecting the urine in two separate amounts by catheter at exactly timed, usually hourly intervals. On one day the renal function was estimated without the spinal anesthesia as a control. One to several days later, the urea clearance was again measured by beginning the observation periods about ten minutes after procaine hydrochloride was injected and coinciding with the beginning of the maximal fall in blood pressure.

Spinal anesthesia was induced by the method described by Maxson (6). The dose of procaine hydrochloride employed was usually 150 milligrams. In a few instances a dose of 100 milligrams was used. The dose of procaine hydrochloride used on each patient is indicated in the tables. In all cases a "hyperbaric" solution was used (6). One hundred and fifty milligrams of procaine hydrochloride were dissolved in 3 cc. of cerebrospinal fluid; doses of 100 milligrams were dissolved in 2 cc. of cerebrospinal fluid. These solutions are 5 per cent in strength and have a specific gravity of 0.008 higher than that of cerebrospinal fluid. After the rapid injection of the procaine hydrochloride solution, the patient was placed flat on his back immediately. Observations of the blood pressure levels, the sensory levels with a pin-prick, and the motor capacity for voluntary movement were begun. As soon as motor paralysis to the extremities was complete, the sensory paralysis had also reached the highest level, and the drop in the blood pressure was maximal. At this point the urea clearance periods were started. Observations of the blood

pressure levels, motor capacity, and sensory levels were continued at ten minute intervals for two-hour periods.

In the entire series of cases there were no patients with heart failure. In a few doubtful cases, venous pressures were measured. These were found normal.

Generally fluid intake was 200 to 250 cc. of water by mouth at the beginning of the test and at the end of the first hour. In two cases (A. H. and D. R.) approximately 400 cc. were given at the beginning and in the middle of the two-hour observation period. In other patients the fluid intake was varied from the above amounts to insure at least a minimal output of 2 cc. of urine per minute. The water intake was the same during the control and experimental periods in any patient.

The urea clearance was calculated according to the "Maximal Clearance" formula when the output of urine was 2 cc. or more per minute and according to the "Standard Clearance" formula when the output of urine was less than 2 cc. per minute. The figures in the column designated "Average Urea Clearance %" in the tables were arrived at by calculating the urea clearance for the two-hour period. They do not represent a numerical average of two one-hour periods.

RESULTS

Twelve patients with normal blood pressures were studied as controls. The pertinent information and results of these tests are summarized in Table I and Figures I, II and V. One of the notable results of this study of patients with normal blood pressures was that spinal anesthesia produced either very little drop of blood pressure of short duration; or, as in most instances, no effect on the blood pressure. In addition, the effect of lowering the blood pressure on the renal function was also studied in twenty patients who had a clinical diagnosis of essential or malignant hypertension. Some of the hypertensive patients had normal renal function, others had moderate impairment of renal function, still others had marked impairment of renal function, as measured by the urea clearance test, before the induction of spinal anesthesia. The data on these patients are summarized in Table II and in Figures III, IV and VI.

TABLE I. UREA CLEARANCE TESTS BEFORE AND DURING SPINAL ANESTHESIA IN PATIENTS WITH NORMAL BLOOD PRESSURE

Patient	Age	Sex	Urine Volume in cc.				Urea Clearance percent				Average Urea Clearance %		Blood Urea Nitrogen		Blood Pressure	Maximum Drop in B. P. mm. of Hg.		Approximate Duration of Drop in Min.	Mgs. of Procaine	Anesthesia		Diagnosis
			Before Spinal Anesthetic		After Spinal Anesthetic		Before Spinal Anesthetic		After Spinal Anesthetic		Before Spinal Anesthetic	After Spinal Anesthetic	Before Spinal Anesthetic	After Spinal Anesthetic	Before Spinal Anesthetic	Systolic	Diastolic			Motor	Sensory	
			1st	2nd hr.	1st	2nd hr.	1st	2nd hr.	1st	2nd hr.												
D. R.	17	M	38	126	31	53	115	95	66	102	97	84	15.9	11.7	120/80	20	18	Max. drop 10 min. Some drop 1 hr.	150	Complete legs 1½ hr.	5th Rib anteriorly	Asthmatic Bronchitis
S. H.	37	M	440	570	245	670	129	115	117	101	122	109	11.2	11.2	130/90	20	6(?)	Max. 10 min. 10 mm. for about 1 hr.	100	Legs 1 hr.	Umbilicus	Pneumonia VII
J. M.	60	M	90	275	225	450	111	92	122	113	95	118	8.9	7	130/85	8(?)	None	10 min. (?)	100	50% Paralysis legs	¾ to Umbilicus	
L. S.	32	M	310	460	58	300	124	97	114	120	107	100	19.6	13.5	115/85	16 mm. no more than control period	10	1 hour	100	Legs complete 1 hr.	½ way to Umbilicus	Tertiary Syphilis Optic atrophy
R. G.	37	M	180	320	28	68	95	95	653	97	95	81	14	16.2	120/80	28	16	25 min.	100	Paralysis Legs	Above Umbilicus	Peptic Ulcer
J. H.	46	M	60	70	112	238	154	150	131	106	152	119	9.8	10.7	120/80	6	4	35 min.	100	Complete Legs 1 hr.	Above Umbilicus	Influenza
J. F.	34	M	330	250	60	134	103	91	84	94	97	84	12.6	14.9	120/80	28	18	20 min.	150	Complete Legs 1½ hr.	3rd rib anterior	Pneumonia
A. J.	22	M	68	415	255	485	123	124	89	103	109	96	10.8	9.8	110/60	5(?)	0	Uncertain	100	Complete Legs 1 hr.	Above Umbilicus	G. I. hemorrhage cause undetermined
J. S.	26	M	92	355	410	360	116	99	197	106	100	no av.	12.6	15.4	110/80	None Rise 10 to 15 mm.	0		150	Complete Legs 1¼ hr.	Xiphoid	Undetermined
O. H.	29	M	63	110	70	180	132	130	141	117	130	113	14.9	15.4	110/80	None Perhaps 5	None Perhaps 5		100	Not Known	Not Known	Pneumonia
A. H.	25	F	180	260	860	452	96	110	101	89	103	95	7	9.3	120/80	Questionable 10 never below control	10 (?)	Very Gradual	150	Complete Legs 1½ hr.	Above Nipples	Diabetes Mellitus
T. M.	50	M	115	225	270	370	85	94	89	59	90	74	10.3	11.1	125/80	35	22	Max. 40 min. Slight for 2 hours	150	Legs 1 hr.	Above Umbilicus	Inguinal Hernia Diabetes Mellitus

Analysis of the data in Table I shows that the volume of the urine was not uniformly affected by the spinal anesthetic. In five patients the volume of urine was greater before the spinal anesthesia and in seven cases the volume of urine was greater during the spinal anesthesia. The volume of urine as such was probably of no significance.

The fall in blood pressure during the spinal anesthesia was not marked in any patient with a normal pressure before the spinal anesthesia. A fall of 20 to 35 millimeters

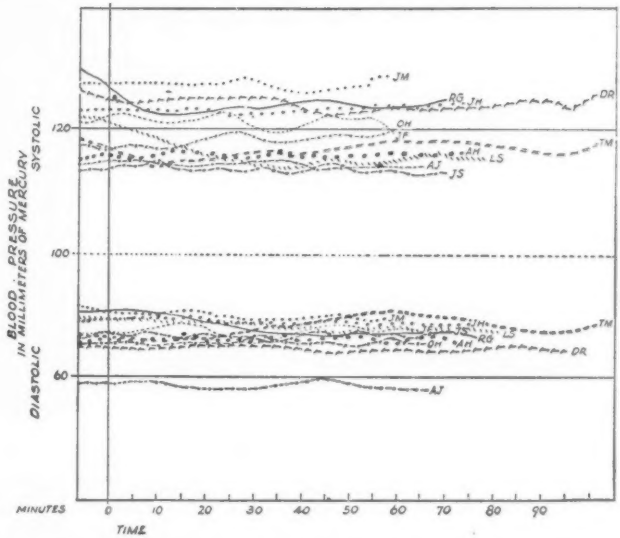

Figure I. Blood pressures on twelve patients with normal blood pressures before induction of spinal anesthesia.

of mercury systolic pressure occurred in only five patients (D. R., S. H., R. G., J. F. and T. M.) (Table I). In the remaining patients with normal blood pressures, there was little or no fall. There was a significant decrease in the urea clearance in four of these five patients in whom there occurred a fall in the blood pressure of the degree mentioned. Patient S. H. showed only a questionably significant decrease of the urea clearance in spite of a drop of 20 millimeters of mercury systolic pressure. The decrease in the urea clearance occurred during the first hour of the test during the period of spinal anesthesia and re-

turned to normal during the second hour in three patients (D. R., R. G. and J. F.). This coincided with the return to normal or nearly normal blood pressure level by the end of the first hour of the test in each of these three patients. It is, of course, usual for the effects of a spinal anesthetic to

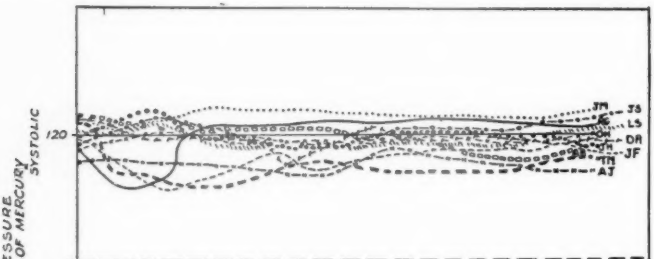

Figure II. Blood pressures on the twelve patients represented in Figure I during spinal anesthesia. It will be noted that there was a slight drop in the blood pressure in a few instances. The spinal anesthesia was completed approximately five minutes before zero time.

completely subside by the end of an hour. Patient T. M., however, showed significant decrease in the urea clearance during the second hour of the "anesthesia" period. We explain this as being due possibly to a sustained drop of 28 millimeters of mercury systolic pressure during the second hour of the period of spinal anesthesia in addition to a maximal fall of 35 millimeters of mercury systolic pressure during the first hour of this period. A study of the urea clearance values summarized in Table I justifies the conclusion that spinal anesthesia, unaccompanied by a significant drop in the blood pressure, does not diminish the urea clearance.

Table II contains the data obtained from and information pertinent to 22 estimations of the urea clearance of 20

TABLE II. UREA CLEARANCE TESTS BEFORE AND DURING SPINAL ANESTHESIA IN HYPERTENSIVE PATIENTS

Patient	Age	Sex	Urine Volume in cc.				Urea Clearance percent				Average Urea Clearance%		Blood Urea Nitrogen		Blood Pressure	Maximum Drop in B. P. mm Hg. during Spinal Anesthetic		Approximate Duration of Drop in Minutes	Mgs. of Pro. caine	Anesthesia		Diagnosis
			Before Spinal Anesthetic		After Spinal Anesthetic		Before Spinal Anesthetic		After Spinal Anesthetic		Before Spinal Anesthetic	After Spinal Anesthetic	Before Spinal Anesthetic	After Spinal Anesthetic	Before Spinal Anesthetic	Systolic	Diastolic			Motor	Sensory	
			1st	2nd hr.	1st	2nd hr.	1st	2nd hr.	1st	2nd hr.												
L. C.*	41	F	510	390	8	285	70	53.5	Discard	71.4	62		10.7	11.6	240/140	108	54	50-108 one hour 40-50 remainder	100	Legs 1 hr.	Xiphoid	Hypertension Heart Disease
L. C.*	41	F	510	390	235	520	69	53	61	66	62	64	10.7	11.6	240/140	100	40	80-100 one hour 20-60 remainder	100	Legs 1 hr.	Xiphoid	Hypertension
L. R.	66	M	78	136	21	37	101	85	80	97	87	89	14.2	14.2	170/90	64	25	40-60 mm. drop for entire two hours	100	Legs 1 hr.	Xiphoid	Essential Hypertension
L. W.	56	F	235	470	21	245	79	79	21	66	79	42	15.8	20	240/115	130	46	130-70 first hour 70-30 second hour	100	Legs 1 hr.	Xiphoid	Hypertensive Ht. Disease Essential Hypertension
W. G.	64	M	69	130	3	94	70	60	19.3	44	61.5	33.2	19.2	16.3	190/90	95	30	60-95 mm. 1st hr. 30-60 mm. 2nd hr.	100	Legs 1¼ hr.	½ way to Xiphoid	Hypertension Hypertensive Ht. Disease
J. M.	48	M	115	117	8	80	39	37	11.4	27.9	38	21.6	29	23.8	258/150	178	98	Maximum 30 minutes 60-100 mm. 1½ hrs.	150	Legs 1 hr.	Xiphoid	Essential Hypertension Malignant phase
J. B.	65	M	154	245	No specimen	307	66	86	For 55	2 hr. period	75	55.6	19.1	18.9	190/120	96	54	50-96 one hr., 30-50 remainder of test period	150	Legs 2 hrs.	Above Nipples	Essential Hypertension
R. S.	53	F	425	325	67	58	83.5	38?	18.2	20.2	?38	19.1	18.6	19.0	140/98	85	54	Marked drop 1 hr. Hypertension 2nd hr. Drugs	100	Legs 1 hr.	Nipples	Chronic pyelonephritis with contracted kidneys. Mild Hypertension
M. C.	50	F	232	335	44	70	63	65	72	70	64	71	9.6	14.7	155/105	34	32	Significant drop 1½ hrs.	100	Legs paralyzed 80 min.	Umbilicus	
E. W.*	55	F	450	293	12.5	70	73	62	13	60	67.5	44	9.8	14.3	214/124	100	50	56-100 mm. 1st hour 20-50 mm. 2nd hour	100	Legs 1½ hr.	Nipples	Essential Hypertension Diabetes mellitus
A. J.	22	M	340	520	305	580	95.4	96.6	125	137	96	131	10.4	10.5	170/104	18	8	Some drop 1½ hrs.	100	Legs complete 1¾ hr.	Nipples	Essential Hypertension
S. S.	45	F	35	30	22	40	79	74	53.4	73.4	76.5	73.4	8.3	10	200/130	42	30	10 min. 20-40 mm. 40 min. 10-20 mm. for remainder	100	Legs complete 1¼ hr.	Umbilicus	Mild Hypertension
A. K.	47	F	340	450	1.6	46	78	103	6	30.2	91	22.4	7.9	7.7	195/110	84	50	60-80 mm. drop 1st hr. 14-60 mm. drop 2nd hr.	150	Legs complete 80 min.	Above Nipples	Fibroid of uterus. Essential Hyper. Diabetes Mellitus
M. W.	38	F	300	580	208	420	74	76	93.5	67	75	80	14.4	16.8	160/110	42	26	Maximum 20-30 minutes 20-35 mm. 1 hour.	150	Legs 1 hr.	Almost to Clavicles	Essential Hypertension

(Continued on next page)

TABLE II. UREA CLEARANCE TESTS BEFORE AND DURING SPINAL ANESTHESIA IN HYPERTENSIVE PATIENTS—(Continued)

Patient	Age	Sex	Urine Volume in cc.				Urea Clearance percent				Average Urea Clearance%		Blood Urea Nitrogen		Blood Pressure	Maximum Drop in B. P. mm Hg. during Spinal Anesthetic		Approximate Duration of Drop in Minutes	Mgs. of Pro. caine	Anesthesia		Diagnosis
			Before Spinal Anesthetic		After Spinal Anesthetic		Before Spinal Anesthetic		After Spinal Anesthetic		Before Spinal Anesthetic	After Spinal Anesthetic	Before Spinal Anesthetic	After Spinal Anesthetic	Before Spinal Anesthetic	Systolic	Diastolic			Motor	Sensory	
			1st	2nd hr.	1st	2nd hr.	1st	2nd hr.	1st	2nd hr.												
J. S.	48	F	56	420	96	132	98	81.4	47.6	62.2	76	53	9.9	10.2	220/120	60	36	40-60 mm. for 30 min. 10-40 mm. for 1 hr.	150	Legs paralyzed 1¼ hr.	Above Nipples	Essential Hypertension
O. B.	53	F	340	540	200	300	107	70	45.4	75	88	60	17.7	16.1	240/124	114	32	Maxi. drop for 40 min. 30-90 mm. for 40 min.	100	Legs 50 min.	Nipples	Hypertension
L. J.	38	F	550	415	455	280	111	117	111	82.5	114	97	7.9	7.7	185/130	14	15	Gradual and slight drop for 80 min.	100	Legs 50 min.	Xiphoid	Essential Hypertension
I. G.	55	F	550	490	204	505	76.5	75.5	53	81	76	67	9.6	8.9	180/120	40	36	Gradual 30-40 mm. 30 min. 10-25 mm. for remainder	150	Legs 1 hr. 20 min.	Nipples	Essential Hypertension
M. Ca.	37	F	540	380	142	220	115	108	86.5	99.5	112	93	7.8	8.9	215/135	66	36	At least 40-50 mm. for entire 2 hours	150	Legs paralyzed 1 hr.	Above Nipples	Essential Hypertension Syphilis III
J. A.	64	M	90	265	58	105	74.5	70	64	78	70	71	14.9	13.1	170/110	40	25	Maximum 20 minutes 1 cc. Adrenalin given	150	Legs 1½ hr.	Nipples	Essential Hypertension
V. D.	47	F	80	380	81	58	59	72	22	40	59	31	16.5	16.3	250/142	136	48	90-136 for 50 minutes 18-60 mm. remainder	150	Legs 1 hr. 25 min.	Nipples	Essential Hypertension
E. W.*	55	F	450	293	46	36	73	62	35.7	29.6	67.5	32	9.8	13.2	220/120	140	80	20 min. drop of as much as 110 systolic, additional 25 min.	150			

* Determinations ran on the same patient at different times.

patients with hypertension during spinal anesthesia. In every patient in this group the urine volume was greater during the control period than it was during the period of spinal anesthesia. This difference was not marked and probably was not significant because of the adequate volume of urine in both the control and experimental periods. In patients L. R., L. W., J. M., J. B., M. C., E. W. (on two occasions), and A. K., however, there was a marked difference between the volume output in the control and experimental periods. This was particularly noted during the first hour of the two-hour experimental period. This

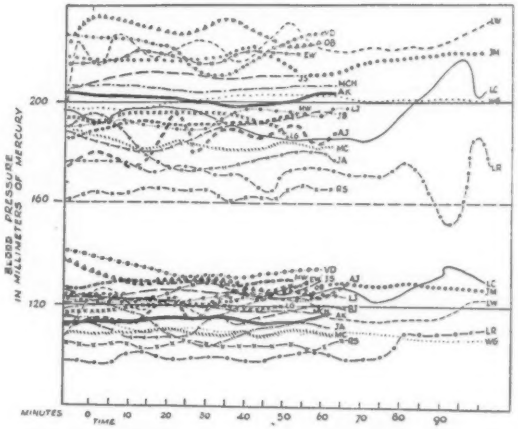

Figure III. Blood pressure on twenty-two patients with hypertension before induction of spinal anesthesia.

coincided with the recovery of the blood pressure by the end of the first hour of the experimental period. This discrepancy in the volume of the urine output during the two separate hours of collection was not due to technical errors of collection because the urine samples were collected by an in-dwelling catheter. The decreased outputs of urine and the diminished urea clearance values are, therefore, due to the effects of the spinal anesthetic.

The data in Table II may be conveniently studied by dividing the cases into three groups: those showing normal urea clearance, those showing moderate reduction of urea

clearance, and those showing severe reduction of urea clearance before the spinal anesthesia.

L. R., A. J., L. J. and M. Ca. are representative of the first group. Patient L. R. showed a significant drop of 64 millimeters of mercury for the entire period, but showed only a slight decrease in urea clearance. A. J. showed no decrease in the urea clearance during spinal anesthesia. There was a drop of only 18 millimeters of mercury in the systolic blood pressure, however, L. J. showed only a slight decrease in urea clearance, but this patient likewise showed a small drop of 14 millimeters of mercury in the systolic blood pressure during the experimental period. It should

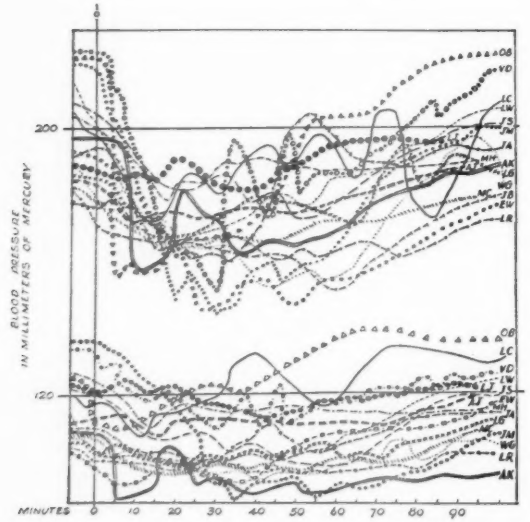

Figure IV. Blood pressures on the twenty-two patients represented in Figure III during spinal anesthesia. Note the drop in blood pressure in many instances. The spinal anesthesia was completed approximately five minutes before zero time.

be noted that the blood pressures of these three patients: L. R., A. J. and L. J., were only moderately elevated, being 170 in two cases and 185 in the other. Patient M. Ca. had a definite decrease in the urea clearance, particularly during the first hour of the experimental period as well as the

two-hour average. In this patient the initial blood pressure was higher (215 systolic, 135 diastolic) than it was in the other three patients. The fall in pressure due to the spinal anesthesia was also considerable, being 66 millimeters systolic and 36 millimeters diastolic of mercury.

It appears from the study of these four patients that a significant fall of blood pressure in a patient with only moderately severely hypertension will be associated with a decrease in the urea clearance, even though the urea clearance values were normal before the spinal anesthesia. It should be emphasized that the blood pressure in each of these four patients was well within or above normal limits after the fall.

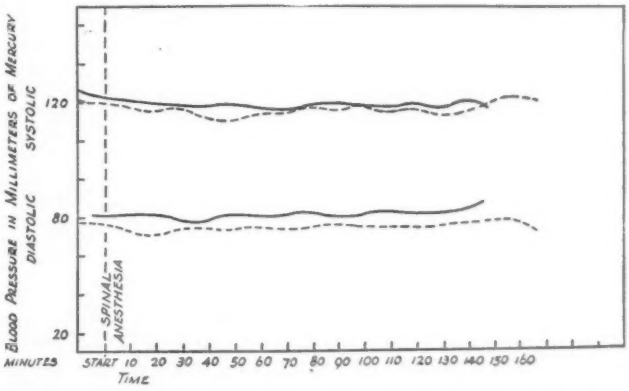

Figure V. Solid lines represent the average of the systolic and diastolic blood pressures on the twelve patients with normal blood pressures shown in Figure I. Broken lines indicate averages of the systolic and diastolic blood pressures on the twelve patients shown in Figure II. Solid lines—before spinal anesthesia; broken lines—during spinal anesthesia. The very slight drop in the blood pressure during anesthesia is noted but these slightly lower levels of blood pressure were present before the spinal anesthesia and after the effects of spinal anesthesia had worn off.

Patients L. W., W. G., J. B., R. S., E. W. (on two occasions), S. S., A. K. and L. G. are representative of a second group, which showed moderate decrease in the urea clearance before the spinal anesthesia; and which showed from a marked to a further decrease in the urea clearance values during the spinal anesthesia. The decrease in the urea clearance was most marked during the first hour of the experimental period. This corresponds to the period of the greatest drop in the blood pressure. Patient L. W.

exemplifies this very well as shown by a drop in the urea clearance from a value of 79 per cent during the control period to a value of 21 per cent during the first hour of the

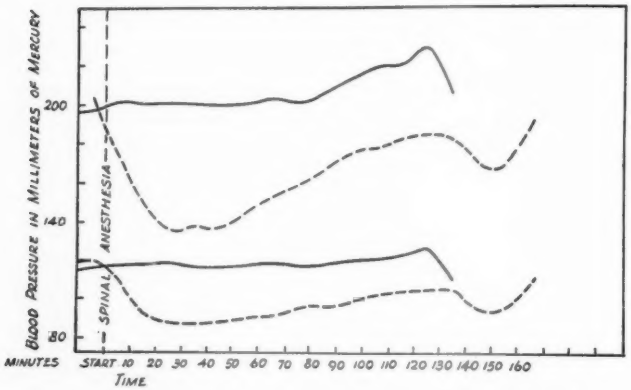

Figure VI. Solid lines represent the average of the systolic and diastolic blood pressures on the twenty-two patients with hypertension shown in Figure III. Broken lines indicate averages of the systolic and diastolic blood pressures on the twenty-two patients shown in Figure IV. Solid lines—before spinal anesthesia; broken lines—during spinal anesthesia. The average marked drop during spinal anesthesia is evident.

experimental period. The latter value had risen to 66 during the second hour with the return of the blood pressure toward normal. Patient A. K. also exemplifies this very well with a drop from an average of 91 per cent urea clearance during the control period to a value of 6 per cent urea clearance for the first, and 30 per cent urea clearance for the second hour of the experimental period. The other cases referred to demonstrate the same point though not so well.

A third group is represented by Patients J. M. and V. D. who had moderate or marked decrease in urea clearance before the spinal anesthesia with a still further decrease in the urea clearance values during spinal anesthesia.

In practically all hypertensive patients, a marked drop in the blood pressure was associated usually with a marked fall in the urea clearance. The one exception to this was patient L. C. (second test) who failed to show a decrease in urea clearance despite a drop of 100 milli-

meters of mercury systolic and 40 millimeters of mercury diastolic. No explanation for this is available at this time.

Attention should be called to the profound and precipitate falls in blood pressure produced by the spinal anesthetic. In one patient, J. M., a fall of 178 millimeters of mercury systolic and 98 millimeters of mercury diastolic was produced. This was the most extreme in the series. There were, however, eight instances of falls of 100 or more millimeters of mercury systolic pressure. And there were twelve patients in whom the systolic pressure dropped 75 or more millimeters of mercury.

The fall in blood pressure induced by the anesthesia was excessive in the second study on E. W., at which time the systolic pressure fell to 80 millimeters. The fall in urea clearance in this instance was not as great as it was in the first study of E. W. when the systolic blood pressure fell from 214 to 114 millimeters of mercury. The latter figure, however, was still within the normal range. It should be emphasized that most of the profound falls in blood pressure resulted in levels which were still within the limits of normal blood pressures. For example, L. C., L. C., L. W., E. W., O. B. and V. D. showed a fall of 100 or more millimeters of mercury systolic pressure. The systolic pressures, however, remained between 110 and 140 millimeters of mercury.

DISCUSSION OF RESULTS

From these studies it seems clear that the renal function, as measured by the urea clearance test, is usually decreased by a fall of blood pressure produced acutely by the subarachnoid injection of procaine hydrochloride. This occurs in both normal and hypertensive individuals.

We wish to emphasize that these are acute experiments. While we doubt that the results would be different with a prolonged profound fall in the blood pressure, it is entirely conceivable that certain adjustments might be effected in the prolonged falls that are not operative during the acute experiments.

The effects of spinal anesthesia on renal function are secondary to the fall of blood pressure. This is well shown in the group of normal patients in whom the urea clear-

ance studies showed but little change during the period of spinal anesthesia. There were several exceptions in whom there were slight reductions of urea clearance values associated with moderate falls in the blood pressure levels. Procaine hydrochloride as a spinal anesthetic agent does not adversely influence urea clearance values. This is shown in a different manner by a study of the hypertensive group. It can be readily seen by reference to Figures IV and VI and Table II. These show that the blood pressure is usually rising by the beginning of the second hour of the two-hour period under spinal anesthesia. Coincident with this rise in blood pressure is a rise in the urea clearance values during the second hour.

The results of these studies have obviously therapeutic implications. Decreased renal function regularly attended the falls in the blood pressure in the group of hypertensive patients studied. It is emphasized again that these results have been obtained during falls of blood pressure of short duration. They should be extended by observations of the renal functions of hypertensive patients during prolonged periods of diminished blood pressure. If our results of decreased renal function are confirmed when produced by prolonged falls in blood pressure, it is obvious that symptomatic therapy directed at decreasing the blood pressure may be unwise.

Without discussing the wisdom of various surgical procedures on the sympathetic nervous system as a means of treatment of hypertension, it is suggested that spinal anesthesia with procaine hydrochloride may be valuable as a preliminary procedure to test the extent to which the blood pressure may be made to fall by interrupting the sympathetic pathways.

REVIEW OF LITERATURE

Page (2b) failed to find any decrease in renal function as a result of either a spontaneous fall in blood pressure, sodium thiocyanate, therapy, or intramuscular injection of collodial sulphur. Reference has already been made to the question of results observed when the blood pressure has been caused to fall by agents circulating in the blood. In addition it may be noted that only six patients were studied, two of whom were hypertensives, two nephritics and two were cases of malignant hypertension. Furthermore in

some of Page's cases the blood pressure was no lower after therapy than it was during some of the control periods. The extent of fall in the blood pressures was not comparable to that produced in our studies.

Reid (2a) found no decrease in renal efficiency as the result of lowering the blood pressure with nitrites. Here, again, the use of drugs may be questioned. Furthermore, the "urea concentration" test was employed as the measure of renal function, the fall in blood pressure in many instances was not marked, and in no instance was there a fall from high to normal levels of blood pressure.

Page and Heuer (3a and 3b) found no change in the urea clearance of one patient with chronic nephritis and one patient with hypertension after denervation of the kidneys. No change in the blood pressure resulted in either patient from the renal denervation.

Page and Heuer (3c) reported no change in the urea clearance of one patient whose blood pressure had been reduced from a systolic pressure of 200 milimeters of mercury to normal levels following section of the anterior spinal roots from the sixth thoracic to the second lumbar levels. The capacity of this patient's kidneys to concentrate urine was somewhat impaired, however. The results in this one case is contrary to those we have obtained in our studies. We have no explanation for the difference in results.

Freyberg and Peet (3e) have obtained results with bilateral splanchnicectomy in hypertensive patients that are at variance with those we have obtained by a method which, in effect, is a functional splanchnectomy produced by the spinal anesthesia. They state, "These observations show that in cases of primary hypertension, satisfactory renal function is not dependent on the high blood pressure; . . ." Our analysis of their data does not wholly warrant this conclusion on their part. Some of their data show improvement in the urea clearance with a fall in blood pressure. On the other hand the renal function of many of their patients (numbers 2, 3, 5, 6, 10, 12, 13, 14, 16, 17, 18, 22, 23, 24, 31, 40, 41, 42, 43, 47) was not studied with urea clearances at the height of the blood pressure fall soon after the operation. In patient No. 12, there was a progressive increase in urea clearance values as the blood pressure increased

toward pre-operative levels. In the light of our results obtained acutely with spinal anesthesia, it would have been desirable to have urea clearance studies on the above mentioned twenty-one cases at the time that the blood pressures were at the lowest levels. Still other patients (numbers 1, 4, 8, 27, 28, 30, 38) of Freyberg and Peet showed a marked decrease in the urea clearance at the lowest level of the blood pressure. In patient No. 1, for example, the urea clearance fell from 106 to 58 per cent and later returned to the previous level. In patient No. 4, the urea clearance fell from 87 to 38 per cent. The urea clearance was 38 per cent two months post-operatively and finally returned to previous levels. It is to be emphasized that these falls in urea clearance were encountered early in the post-operative course and that the urea clearance tended to recover in time.

Page and Heuer (3d) observed no change in renal efficiency, as measured by the urea clearance or the ability to concentrate urine, from the partial denervation of the kidneys or from the fall in blood pressure produced by section of anterior nerve roots in patients with essential and malignant hypertension. While the resulting fall in blood presure was from 30 to 60 millimeters of mercury systolic pressure in some of their patients, in many others it was only 12 to 15 millimeters of mercury. But in *none* of their patients did the blood pressure fall to normal levels.

SUMMARY

The effect on the renal function of lowering the blood pressure has been studied in twelve patients with normal blood pressures and in twenty patients with hypertension. Spinal anesthesia with procaine hydrochloride has been used as a method of lowering the blood pressure. The urea clearance test has been used as a measure of renal function. The possible lack of wisdom of symptomatically reducing the blood pressure of hypertensives, particularly to normal levels, has been mentioned and briefly discussed.

CONCLUSIONS

Spinal anesthesia with procaine hydrochloride usually produces a profound fall in the blood pressure of hypertensive patients.

The fall in blood pressure usually results in a marked decrease in renal function, even though the resulting pressure is within normal limits. The renal function returns to its previous level with the return of the blood pressure to previous levels.

The subarachnoid injection of procaine hydrochloride resulting in motor paralysis to the legs and sensory paralysis to high chest levels, does not cause a decrease of renal function unless attended by a sufficient drop in the blood pressure.

The decrease of the blood pressure of hypertensive patients to normal levels by symptomatic measures is probably not desirable.

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A RAPID AND SIMPLE RELIEF STAIN FOR THE DEMONSTRATION OF BACTERIAL CAPSULES

GERALD YOUNG AND B. BERYL BREWER*

Since the presence or absence of a capsule continues to be an important criterion in the identification of several common pathogenic organisms, a modification of Benian's relief stain for bacteria and spirochaetes has proved an excellent method for the demonstration of this structure. It differs from the original method in that a very thin film is made rather than a tolerably thick one, and the differentiating solution used is a 0.5 per cent solution of HCl in 95 per cent alcohol saturated with a bacterial stain rather than the 1 per cent HCl in absolute alcohol. The stain for the background is the same as that used originally.

Method:

1. Suspend a loopful of organisms in a small drop of a 2 per cent aqueous solution of Congo red, mix well, spread as thinly as possible, and air dry.

2. Stain for three minutes in a Coplin jar in a saturated solution of acid fuchsin in acid alcohol (0.5 per cent HCl in 95 per cent ethyl alcohol).

Note: Stain should be kept covered when not in use.

3. Shake off excess stain and blot dry immediately, to avoid crystallization of the acid fuchsin on the slide.

The result is that the bacteria are stained in contrast to the background, leaving the capsule only instead of both the capsule and the organism, in relief. The organism is light red against a pale blue background. See photomicrograph of Type I pneumcoccus from the peritoneum of mouse, showing large, well defined capsules. The bacterial stain found to be most satisfactory is acid fuchsin, although other simple stains such as orange G or light green may be used with but slightly less success.

In addition to the fact that smears may be made directly from the infectious material or in some instances from routine culture media, the advantages of this staining method are the simplicity and rapidity with which it is

*From the Departments of Preventive Medicine and Pathology, University of Texas Medical School, Galveston, Texas. Submitted for publication February 3, 1943.

accomplished, the stability, and availability of the staining solutions and the uniform results.

The above technique has been tested on the following organisms: several types of *Streptococcus pneumoniae, Klebsiella pneumoniae* and *Clostridium welchii.* All organisms give a well stained cell and a sharply defined capsule.

Acknowledgements: One of us (Gerald Young) wishes to express his gratitude to Drs. V. T. Schuhardt and I. M. Lewis of the Department of Botany and Bacteriology of the University of Texas, Austin, Texas, for their interest and guidance in the earlier phases of this work.

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THE UNIVERSITY OF TEXAS HEALTH PROGRAM

. . . A STATEMENT BY THE VICE-PRESIDENT IN CHARGE OF MEDICAL EDUCATION*

In August, 1942, President Homer P. Rainey announced a proposal for a state-wide health program to be administered by the University of Texas. This challenged my interest sufficiently for me to accept an invitation to come as Vice-President of the University to take charge of the proposal. Now I'm thankful for the chance to work with Texans in a project worthy of them. And I'm grateful for this opportunity to discuss this health program.

OUR STATE, OUR UNIVERSITY, OUR HEALTH

Intelligent Americans understand that we must work together for our commonwealth—our states, our universities, our health. We form our states for the purpose of co-operating together for the benefit of us all, for pooling our resources, for mutual aid and protection for each of us, and for agreeing on the least common denominator of what we allow each other to do. As people appreciating the importance of knowledge in the accomplishment of our purposes, we support state universities. Our universities exist to acquire knowledge (research), to preserve it (in libraries), to distribute information so that we may benefit from it, and to pass it on to our children through teaching. We all desire long and good health. Our increasing knowledge has made it possible for us to live longer and to be more healthy, efficient, and satisfied. Our health program exists for the purpose of making this knowledge easy for us to get, so that we may apply it to our common welfare.

OUR ADDED HEALTH RESPONSIBILITIES IN WAR.

In our present crisis, however, we have an added responsibility in utilizing the facilities of our University for the promotion of our good health. We must keep ourselves at top mental and physical efficiency, and we must learn how to do this without belly-aching or headaches. Many of us may even have to learn how to eat to best advantage.

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* This statement made possible for publication in the Dallas News of January 1, 1943, through the co-operation of friends of the University of Texas, for its outstanding achievements in the field of education and medicine.

We are host to a greater number of men in military training, and to a greater number of military organizations and efforts, than any other state in our country. We also have peculiar advantages in diversity of climate, in the abilities of our people, and in variety and amount of contact with different people throughout the world. These circumstances make it possible for us to contribute powerfully toward the health factors that are necessary for winning and keeping the kind of a world we want.

It is becoming increasingly clear to intelligent people that co-operation has greater advantages than competition, either locally, internationally, racially, or in any other way. We are still in the painful process of learning this elemental biological principle. It is necesary, however, that we grasp it if we are to develop the only sort of a world fit for intelligent people to live in. We must in order to get the world we want, keep ourselves and the rest of the world in good health for our mutual welfare.

CO-OPERATION IS ESSENTIAL FOR SUCCESS.

In accordance with the purposes of our University, our health program should provide fully for getting, keeping and passing on information on health, the prevention of disease, and the preservation of optimum physical and mental efficiency and satisfaction. Already broad work along these lines is in progress at the Main University campus in Austin, at the Medical Branch in Galveston, at the College of Mines in El Paso and now at the new health center being developed in Houston. It is important for us to co-ordinate these efforts with each other, and with similar efforts in other parts of the state, the country, and the world, in order to avoid unnecessary duplication and competition, and in order to promote efficiency and economy.

OUR CO-OPERATIVE CANCER EFFORT.

As an example, there is need for a co-ordinated program for cancer control in Texas, since there is a relatively high incidence of this disease in this area. The Clayton Foundation supports fundamental research on the causes of cancer at Austin, under the direction of Professor Roger Williams, and Professor T. S. Painter.

Our Legislature, through the University's regents, and the M. D. Anderson Foundation, are establishing a hospital and laboratory for cancer research in Houston under the direction of Doctor E. W. Bertner. This will devote itself chiefly to studying improved methods for the rapid diagnosis of cancer and for co-operation with doctors throughout the state in order to assist in early detection and proper treatment of cancer.

The Tumor Clinic at our University's Medical Branch Out Patient Department is designed to co-operate with similar clinics and with doctors throughout the state in difficult diagnostic problems. It also co-operates with Doctor Williams' group in Austin, and the Houston group in supplying clinical material for research.

OUR CO-OPERATIVE MENTAL HYGIENE EFFORT.

Another pertinent example relates to the state-wide effort to control mental disease and to prevent mental disorder by promotion of mental and emotional stability.

In this promotion of mental health the Hogg Foundation at the University of Texas, under the direction of Doctor Robert L. Sutherland, brings the best experts available to us for teaching and training in mental hygiene. It co-operates closely with the Psychiatry Department of our University Medical Branch, under the direction of Doctor Titus Harris, in furthering the prevention and management of mental disease. There is co-ordination with our State Hospitals in handling mental disease, and with the mental hygiene program of the United States Public Health Service.

Since the mental attitude and emotional maturity of our people will be important factors in getting the kind of a peaceful world we want, the effects of our mental hygiene program may become most significant indeed. The more interest and support it obtains from our citizens, the more impressive will be its success. It offers the opportunity to us all to improve our mental outlook. All we have to do is take advantage of the opportunities offered to us, by attending the free lectures provided, by reading and studying the material offered, by training ourselves by the methods described to us, and by practicing emotional control.

Self-knowledge, self-control, self-discipline, self-confidence, self-instruction—these are the foundation of our commonwealth. These are the "disciplina" of the motto of the University of Texas. *"Disciplina Praesidium Civitatis."* And no one can pour them into us. We have to go out to get them for ourselves. Our University health program will help.

CHILD HYGIENE AND PUBLIC HEALTH.

A program in child hygiene, similar to that discussed for mental hygiene, is under consideration by our University as part of its health program. Associated with both of these efforts, may be a co-ordinated program for sanitary improvements throughout this area, designed to prevent epidemics, reduce possibility of rat and insect borne diseases and to help people generally to live more comfortably and decently.

A broad public health effort may come as part of the teaching and service portions of the health program, if satisfactory support can be obtained.

Public health teaching and service are becoming increasingly necessary in Texas in order to take care of the rapidly changing conditions incident to urbanization and industrialization. An industrial hygiene program is under way in co-operation with major industries through the state and with various public and private agencies. Special training and service functions may be necessary to provide adequate medical care for people living in rural areas where there is not sufficient population to support private physicians or nurses. In this matter, all of us may have to co-operate to provide the necessary medical care for the people living in sparsely settled areas and to prevent possibility of infection spreading from these areas to the more thickly populated centers.

LOCAL HEALTH PROBLEMS BEST HANDLED LOCALLY.

To the intelligent citizen, it must be clear that our University concerns itself with broad factors affecting our citizens generally. Its health program should be geared to this concept. It is unwise for our University, for example, to concern itself with strictly local health problems which every community should prepare to handle for itself.

Such matters as venereal disease control, tuberculosis, slum clearance, blood banks, hospitals for the management and care of mentally ill, crippled children, and chronic indigent sick, are more appropriately handled by local communities than as part of our University health program.

RESEARCH, TEACHING AND SERVICE FUNCTIONS OF OUR UNIVERSITY MEDICAL BRANCH.

When special problems of diagnosis or treatment arise, requiring special methods or the services of experts, the facilities of the University health program are available. These special diagnostic and treatment services are centered in our University Medical Branch, in Galveston. Special teaching and research along these lines, if it is pertinent to the broad problems involved, are also centered in the Medical Branch.

From the general medical training center at Galveston, contact is made with hospitals, clinics, and other agencies throughout the state. Liaison is also furnished through this center with other state, national and international health efforts. It collects knowledge on health from all over the world for our benefit and passes on what is discovered, to be used by anyone who may wish.

It is appropriate, in view of the excellent facilities already provided, that general medical research and instruction proceed at the Medical Branch. This may satisfactorily remain the University center for basic instruction in medicine, nursing, public health and auxiliary fields.

Much of this teaching and training of our needed doctors, nurses, dentists, druggists and public health officers, may be under military control for the war period and after. We can all help by cheerfully pitching in together to promote the necessary medical training program. We must realize that only the best intellectually qualified young people are suitable for a medical career these days. Such a career takes tough and top brains. We cannot tolerate mediocrity in medicine. We can help by promoting an adult outlook in our teen-agers, and by stopping our sentimental drooling over them.

Under Dean F. C. Elliott, the Texas Dental College in Houston has become one of the best in the country. Its incorporation into the University's health program would

assist materially in co-ordinating the various special fields relating to health so that the professions concerned might work more effectively together. In accomplishing this desired end, it is helpful for students in dentistry, pharmacy, medicine, nursing and public health to be associated together in connection with their training, so that they may come to know each other and to understand each others problems, interests and responsibilities.

As a part of the larger health program for Texas there should be developed a School for Public Health for the training of public health officers and nurses, and for research in the promotion and control of public health. This might become associated with the state's agricultural and veterinary interests, including the University's Brucellosis research, with respect to the inter-relations of diseases of animals and man, and to the promotion of a more optimum dietary and nutrition for our people.

PIONEERING IN NEW HEALTH FIELDS: GEOGRAPHIC MEDICINE AND GERIATRICS.

Two great opportunities exist in Texas for world-wide extension of our health program. The first relates to special research and training in geographic medicine. The second deals with the care of the aged. The immediate importance of the former is apparent from the fact that our soldiers are now fighting in all parts of the world. They are coming in contact with diseases that vary with climate and with geographical condition. It is not enough to put emphasis on tropical medicine, since many of our fighters will be subjected to the peculiar health problems of the arctics. Here is an almost unexplored field. With its varied climate Texas offers a fine place for the study of geographic medicine, and for effective training in it.

The peculiar features existing in Texas favorable to the intensive study of geographic medicine are (1) as great a variety of climatic and geographical conditions as may be found in any single economic area, (2) close contact with all parts of the world through shipping and commerce, (3) a greater diversity of diseases influenced by climate than may be found elsewhere in this country and (4) a greater number of troops in training than anywhere else in the country.

Relatively small funds would be needed to develop an institute for geographic medicine as part of our health program. Little laboratory research would be required at first. It would be necessary, however, to compile the data available in existing publications from various parts of the world, co-ordinate it and condense it for effective training of our own physicians in the armed forces so that they might profit from it. As particular problems arise these might be investigated by laboratory methods. Teaching laboratories might be necessary for training medical officers in techniques involved in the identification of particular diseases likely to be encountered in different parts of the world.

Another very pressing and appropriate subject for our long-range University health program is concerned with old age. For the first time in the history of humanity we seem to have more people alive over 30 than under. Our increasing knowledge regarding the preservation of good health has made it possible to prolong the life expectancy by many years. This has created an unexpected and acute problem involving economics, politics and sociology. We have not yet developed a satisfactory means of preparing people for old age. If it is desired that older people remain among us with dignity, health and equanimity, special systematic efforts must be made to train them for such a position.

Accordingly, it would be a major contribution of our University's health program were it to include an Institute for Geriatrics, which is the study of the diseases and conditions of old age. There is no such institute in existence anywhere, and its establishment by our University would be a pioneering step of tremendous importance. It deserves the full support of all of us, and it might become a decisive factor in the future development of the kind of a world we want.

LET'S WORK TOGETHER TO BETTER OUR HEALTH

As citizens of Texas we may be proud of our University's health program, and we may feel privileged to participate in such a far-reaching and significant co-operative enterprise. We have a great chance to work together for

the real benefit of all of us, and for the extension of these benefits to peoples all over the world. We have the opportunity to work together in our health program to improve our own efficiency and the health of our troops no matter where they may be serving, in order to win and keep the kind of a world we want. Our medical officers will probably be stationed all over the world for many years to come. We have to prepare to furnish much larger numbers of doctors, dentists, nurses, pharmacists and public health officers than have been necessary so far for the needs merely of our own community. We may feel privileged to assume part of the responsibility of furnishing sufficient numbers of health experts for service throughout the world. In this undertaking we may co-operate efficiently with other public and private health agencies. Texas is fortunate in having an admirable private medical research and training effort in Dallas. Our University health program supplements the work of established public and private health agencies, and is available for effective co-ordination of all health efforts with the purpose of increasing efficiency, and reducing expense. We have the opportunity—let's work together to take advantage of it.

CHAUNCEY LEAKE
Dean and Vice-President of the University of Texas Medical Branch, Galveston.

CALLING ATTENTION TO: ITEMS OF POSSIBLE INTEREST TO FRIENDS OF OUR EFFORT

JANUARY, 1943

1. **Journals:** How about more subscribing for South American medical periodicals? Get lists from consuls. Note the new XIIth **U. S. Pharmacopeia** (Easton, 1942) gives Spanish synonyms? Remember we're North Americans. Britain's Imperial Chemical Industries publishes interesting general science quarterly with appropriate name **"Endeavor,"** and with big name reviews. Academic Press (125 E. 23rd St., New York City) issues two volumes yearly at $5.50 per, the **Archives of Bio-Chemistry.** Contains intriguing article by W. F. Peterson on Weather and Biochemical Variability (1:269 (Dec.) 1942). How's for seeing that co-operative society journals have broad geographic repreresentation on editorial committees in order to prevent dominance by canons of self-justified ins? **Vale** and let's hope soon **Ave** to Francis Packard and the **Annals of Medical History,** suspending after twenty-five years! **Federation Proceedings** will be published even though the Federated Societies will not meet—get your abstracts ready! Edwards Bros. of Ann Arbor announce that Vols. 1, 2 and 3 of **Chemical Abstracts** (the hard ones to get to complete your set) will be lithographed and available. Also—the full fifty-nine volumes of **Beilstein's Handbuch der Organischen Chemie** for $400.

2. **Books:** Adam Hilger (98 St. Pancras Way, London, NW1) issues L. Heilmeyer's **Spectrophotometry in Medicine,** and second edition of R. A. Morton's **Application of Absorption Spectra to Study of Vitamins, Hormones and Co-Enzymes.** Cambridge Instrument Co. (England) issues descriptive pamphlet on the polarograph. G. S. Wilson gives the case for pasteurization of milk (C. Arnold, London, 1942). C. C. Thomas publishes J. Nash's **Surgical Physiology** (Springfield, Ill., 1942). American Council on Public Affairs (2153 Florida Avenue, Washington) offers S. Wilson's important **Food and Drug Regulation.** Richly significant is J. Needham's **Biochemistry and Morphogenesis** (MacMillan, N. Y., 1942, $12.50). S. P. Lucia's brochure, **The Therapeutic Uses of Wine,** (Wine Advisory Bd., San Francisco) is good enough to be expanded to a real book. S. Dali's **Autobiography** is as rare an autopsychiatry as W. E. Leonard's **Locomotive God.** Williams & Wilkins (Balt. 1942) offer A. Mueller-Icham's **Internal Medicine in Old Age.** Interscience (N. Y., 1942) issues Vol. 2 of **Advances in Enzymology.** Columbia Press (N. Y., 1942) publishes J. T. Culbertson's **Medical Parasitology.**

3. **Blood:** F. C. Poles and M. Boycott (like J. R. Upton, San Francisco Blood Bank) report on syncope in blood donors (**Lancet,** 2:531, Nov. 7, 1942). K. E. Boorman & Co., like Tom Kelly of San Francisco, discuss clinical significance of RH factor (**Brit. Med. J.,** 2:538-569, Nov. 7 and 14, 1942).

4. **Biochemorphology:** E. Way urges reading of P. H. Bell and R. O. Robin's swell note (J. Am. Chem. Soc., 64:2905, 1942) showing

bacteriostatic power proportional to negativity of SO_2 groups of N^1 substituted sulfonamides. Also W. Alberts remarks on chemophysics of antiseptics (Lancet, 2:633, Nov. 28, 1942). H. Burton & Co., discuss bacterial development of colors in contact with sulfonamides as evidence of oxidation factors involved in bacteriostasis. C. B. Allsopp (Nature, 150:548, Nov. 7, 1942) reports a water soluble carcinogen derived from 3:4 benzpyrene. H. J. Robinson and O. E. Graessle (J. Pharmacol. Exp. Therap., 76:316, 1942) give full dope on gramacidin, tyrothricin, and tyrocidin.

5. **Industrial Toxicity:** W. C. Hueper's Occupational Tumors and Allied Diseases (C. C. Thomas, Springfield, Ill., 1942) is tops. R. A. Mortensen (J. Ind. Hyg. Tox., 24:285, 1942) shows lead tetraethyl is lung absorbed prop. to conc. about 20 per cent of what reaches alveoli; toxic around 10 mg/kg and rapidly destroyed in tissues. C. D. McCord & Co., (ibid., p. 265) note that while indium in industry offers no risk, its cmpds. are toxic on parenteral injection—1 to 10 mg/kg, with tissue hemorrhage.

6. **Notes:** S. R. Elek and S. D. Selanz (Am. Heart J., 24:281, 1942) recommend 40 mg. papverine HCl IV as safe repeatable test for circulation time—sudden deep inspiration 16 to 27 sec in normals, longer in congestive heart trouble, shorter in hyperthyroidism. H. Lehmann & Co. (Nature, 150:603, Nov. 21, 1942) show amino acids increase sol. of calcium salts, and kidney oxidases decrease it. R. E. Johnson & Co. (J. Nut., 24:585, 1942) show need of B complex for men doing hard work.

FEBRUARY, 1943.

1. **Cancer:** A. Taylor announces successful production of a mammalian tumor by a virus-like principle grown on egg yolk (Science, 97:123, Jan. 29, 1943). J. J. Biesele, H. Poyner and T. S. Painter describe nuclear phenomena in mouse cancers (Univ. Texas Publ. 4243, 1942). Most important and impressive is E. S. Sundstroem and G. Michaels' Adrenal Cortex in Adaptation to Altitude, Climate and Cancer (Univ. Calif. Mem., Berkeley, 1942, 409 pp. in 4to), which would have made a score of hot journal articles. Proceedings Amer. Assoc. Cancer Research appear in February issue Cancer Res. (3:120, 1943).

2. **Historical:** Congratulations to J. H. Gaddum on succeeding to the great chair of pharmacology at Edinburg. He gracefully reviews the development of materia medica there (Edin. Med. J., 49:721, Dec. 1942). H. B. Adelmann edits the Embryological Treatises of Hieronymous Fabricius of Aquapendente (Cornell Univ. Press, 1943). John Fulton prepares Harvey Cushing's Vesalian Notes for the quatrocentennial. John Saunders likewise has ready an annotated translation of the Vesalian China Root. The history of Science Society needs your support: Dues $5.00 per year bring Isis; remit to A. Pogo, Harvard Library 187, Cambridge, Mass.; it's needed for our culture. J. J. Izquierdo brilliantly describes the Zachheim murals on California's Medical History at the Univ. California Medical Center, San Francisco (Mexico City, 1942).

3. **Books:** B. Harrow's **Biochemistry** (3rd Ed., Saunders, Phila., 1943) looks good. C. C. Thomas issues I. G. Macy's **Nutrition and Chemical Growth in Childhood.** The Interscience Publications furnish E. Gellhorn's **Autonomic Regulations** and W. C. Boyd's **Fundamentals of Immunology.** From Columbia Univ. Press comes E. Mayer's **Systematics and the Origin of Species.** Allen, Unwin (London) issue the remarkable discussion aroused by C. H. Waddington on **Science and Ethics,** in which the Bishop of Birmingham, the Dean of St. Paul's, J. Huxley and yours faithfully participate. From the Univ. of Minnesota Press comes C. M. Christensen's **Common Edible Mushrooms.** Williams and Wilkins (Balt.) issue D. Rapaport's **Emotions and Memory.** Cattell Press (Lancaster) put out Vols. 8 and 9 of **Biological Symposia:** R. Redfield's **Levels of Integration in Biological and Social Systems,** and F. C. Koch and P. E. Smith's **Sex Hormones.** Vol. 10, Cold Spring Harbor Symposia appears: **Relation of Hormones to Development.**

4. **Radioactive Elements:** C. Pecher's posthumous classic on the biological effects of radioactive calcium and strontium with a clinical report on their use in bone tumor finally appears (**Univ. Calif. Pub. Pharmacol.,** 2:117, 1942). M. E. Morton and I. L. Chaikoff observe **in vitro** formation of thyroxin by thyroid tissue with radioactive iodine as an indicator (**J. Biol. Chem.,** 147:1, 1943). Symposium on trace elements in relation to health in summarized in **Nature** (151:28, Jan. 2, 1943).

5. **Ends and Odds:** G. G. Villela (**Mem. Inst. O. Cruz,** 37:427, '42) shows normal urinary excretion of riboflavin varies between 76 and 1300 microg. per day. Sulphonamide resistance in gonorrhoea is reviewed by J. Petro (**Lancet,** 1:35, Jan. 9, 1943). L. R. Dragstedt et al report on antagonistic effects of lipocaic and anterior pituitary on fat metabolism (**Am. J. Physiol.,** 138:264, 1943). R. L. Noble claims to have produced resistance in rats to amounts of trauma usually fatal (Ibid., p. 346). J. Bronfrenbrenner discusses physical and chemical agents in allergy (**J. Allergy,** 14:105, 1943). R. Granit proposes a physiological theory of color perception (**Nature,** 151:9, Jan. 2, 1943). N. East's Chadwick Lecture on Prevention and Treatment of Anti-Social Behavior is reviewed in **Nature** (151:9, Jan. 2, 1943). P. G. Fuerstner shows reaction of tubes and ovaries to induced vascular spasm (**Univ. Calif. Pub. Pharmacol.,** 2:105, 1942). D. Burk and R. J. Winzler write on vitamers of biotin (**Science,** 97:57, Jan. 15, 1943). J. H. Sandground notes that p-amino benzoic acid reduces toxicity of old pal carbarsone (USP XII!) and similar arsenicals (**Science,** 97:73, Jan. 15, 1943). R. H. Abrahamson and J. W. Hinton discuss the significance of gastric mucosa as an endocrine gland in gastric carcinoma (**SG&O,** 76:147, 1943). Vol. 1 of a series on Effects of Alcohol on the Individual appears from Yale Press, and shows confusion on etiology of addiction.

MARCH, 1943

1. **New Journals:** From the Brooklyn Medical Press comes **Experimental Medicine and Surgery,** with international editing including **J. J. Izquierdo** of Mexico, and C. J. Wiggers' tight review on the irreversibility characteristic of shock (1:1, 1943), and an interesting series on procaine esterase by B. Kisch et al (1:51-93, 1943). The first number of **Gastroenterology** is dedicated to William Beaumont and contains R. Elman's correlation of cytological and chemical changes in the liver (1:24, 1943). Watch for **Texas Reports on Biology and Medicine,** which will go free to every medical institution library wanting it. First issue will have notes by Cary, Ebaugh, Mira, Gregory, Anigstein and Carlson.

2. **And New Books:** E. M. East continues studies on **Biology in Human Affairs** (McGraw, N. Y., 1943). J. C. Berry describes **A Pioneer Doctor in Old Japan** (Revell, N. Y., 1942). W. F. Boos gallops along **The Poison Trail** (N. Y., 1942). E. Weiss and O. English offer **Psychosomatic Medicine** (Saunders, Philadelphia, 1943). W. R. Cooke's **Essentials of Gynecology** (Philadelphia, 1943) is swell except for no stimulus for further reading. V. Nesfield discusses **Viscosity of Blood and Its Bearing on High Blood Pressures** (Muller, London, 1942). A. S. Pearse gives a neat **Introduction to Parasitology** (C. C. Thomas, Springfield, Ill., 1942).

3. **Psychiatry Clinics:** The Langley Porter Clinic at the University of California Medical Center, San Francisco, was dedicated with excellent remarks by Walter Treadway, Langley Porter, Karl Bowman, et al. Its Out-Patient Department is named in honor of Aaron Rosanoff, who started it. The proceedings should be published. The Menninger Clinic in Topeka, Kansas, steps out with a neat gynecology and obstetrics number of its Bulletin, (free on request). It also supports a monograph series of which D. Rapaport's **Emotions and Memory** is No. 2. Further, Karl Menninger's **Love Against Hate** (N. Y., 1943) is what we need more of.

4. **Chemotherapy:** New diamidino compound, 4:4'diamidino-diphenoxy-propane dihydrochloride (Propamidine) is found very useful in treating acute and chronic septic wounds, and seems almost ideal for first-aid in burns (W. Thrower and F. Valentine; A. McIndoe and A. Tilley; G. Mosley and J. Bentley, **Lancet** 1:133-138, January 30, 1943). H. J. Barber et al note fourfold rise in toxicity of stilbamidine solutions (used in kala azar, I. Napier, **Ind. Med. Gaz.,** 77:321, 1942) on exposure to light (**Nature,** 151:107, January 23, 1943). M. Ehrenstein well summarizes antimalarials (**Amer. J. Pharmacy,** 114:456, 1942). W. Trager's item on reducing malaria susceptability by biotin appeared in **Science** (97:206, February 26, 1943).

5. **Liver:** Pleasant to see J. M. Munoz and L. F. Leloir's note from Buenos Aires on fatty oxidation by liver enzymes (**J. Biol. Chem.,** 147:355, 1943). L. L. Chaikoff, K. B. Eichorn, C. L. Connor show that prolonged feeding of a high fat diet may produce fatty infiltration and liver cirrhosis (**Amer. J. Path.,** 19:9, 1943). M. M. Wintrobe et al say that pyridoxine deficiency causes anemia, convulsions and fatty liver (**Bull. John Hopkins Hosp.,** 72:1, 1943).

6. **Elements:** M. E. Reid well reviews interrelations of calcium and ascorbic acid to sell surface, intracellular substances and physiological action (**Physiol. Rev.**, 23:76, 1943). S. Spiegelman and J. M. Reiner offer important kinetic analysis of potassium accumulation and sodium exclusion in cells (**Growth**, 6:367, 1942). G. E. Sheline, I. L. Chaikoff, H. B. Jones, M. L. Montgomery find that zinc is mostly excreted by gastroenteric tract (**J. Biol. Chem.**, 147:409, 1943).

7. **In General:** V. Menkin isolates factor in euglobulin factor (necrosin) responsible for tissue injury in inflammation (**Science**, 97:165, February 12, 1943). D. Nelson, S. Goetzl, S. Robins, A. C. Ivy confirm J. A. Campbell (**Quart. J. Exp. Physiol.**, 28:231, 1938) that high carrot diet protects rats from lethal effects of low oxygen pressure (**Proc. Soc. Exp. Biol. Med.**, 52:1, 1943). E. E. Nelson describes pressor response to acetaldehyde (**Ibid.** p. 23). M. E. Stevens et al discuss expectorant action of creosote and guaiacols (**Canad. Med. Asso. J.**, 48:124, 1943) R. R. Burtner finally publishes account of aryl acetic acid ester antispasmodics reported by G. Lehman and P. K. Knoefel (**J. Pharmacol.**, 74:217-274, 1942; **J. Amer. Chem. Soc.**, 65:262, 1943). C. H. Sawyer says cholin esterase content is index of functional capacity of neuromuscular aparatus (**J. Exp. Zool.**, 92:1, 1943).

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APRIL, 1943

1. **Books Roll On:** Oleanders (Galveston orchids) to A. W. Ham and M. D. Salter of Toronto for their skillful **Doctor in the Making: The Art of Being a Medical Student** (Phila., Lippincott, 1943). Ditto to Y. Henderson & H. Haggard for a concise 2nd edition of their standard **Noxious Gases** (Reinhold, N. Y., 1943). Ohio State University Development Fund, Columbus, announces English edition of Paul Bert's classic **Barometric Pressure** by M. A. & F. A. Hitchcock at $9.00 prepublication. W. S. Cutting offers a **Manual of Clinical Therapeutics** (Phil., Saunders, 1943). R. D. Herrold briefs the **Chemotherapy of Gonococcic Infections** (St. Louis, Mosby, '43). I. Galdston gives a popular peek **Behind the Sulfa Drugs: A Brief History of Chemotherapy** (N. Y., Appleton, '43) which isn't as informative as M. Silverman's chapters in his **Magic in a Bottle** (N. Y., MacMillan, 1941). C. C. Thomas of Springfield, Ill., offers A. Coca's **Familial Nonreaginic Food-Allergy**, and the **Medical Progress Annuals.** P. Wylie's **Generation of Vipers** (N. Y., '42) makes me wonder. W. Saroyan's **Human Comedy** (N. Y., '43) makes we wishful. J. Fortune & J. Burton's **Elizabeth Ney** (Knopf, N. Y., '43) illustrates many of the points of K. Menninger's **Love Against Hate** (N. Y., 1943), and gives the low down on old Texas.

2. **Nature:** (the magazine) like Univ. of California, celebrates its 75th birthday, & properly notes centenary of MacMillan, its publisher. In recent issues: P. C. Koller shows increased rate of cell division due to quantitative change in nucleic acid synthesis (151: 244, Feb. 27, 1943); B. Macgraith, G. M. Findlay & N. Martin (in West African Force) find evidence for red cell lytic enzyme usually held in check by

inhibitors in tissues & plasma (ibid., p. 252). P. B. Medewar et al find 8-hexenolactone inhibits fibroblastic growth but not epithelial (ibid., p. 195). J. Barcroft et al come back brilliantly by finally showing that sodium acetate is used by mammalian heart & at about same rate as glucose (ibid., p. 304, Mch. 13, '43).

3. **Medicine:** (the magazine) comes across with 3 good reviews in February issue (Vol. 22, No. 1): D. McEachern on thymus in relation to myesthenia gravis; R. Ottenberg & R. Spiegel on non-obstructive jaundice due to chemicals, and G. Martin & M. R. Thompson on intravenous alimentation with amino-acids.

4. **Public Health:** The scientific question about vitamins contributing to physical fitness is finally answered affirmatively by A. A. Harper et al (Brit. Med. J. 1: 243, Feb. 27, 1943). C. A. Mills shows positive correlation between urban air pollution & incidence of respiratory diseases (Amer. J. Hyg., 37: 131, 1943). Say, maybe we have to do more fighting on the home front in this war: Don't we need lots of people with brains and ability to help reduce the alarming increase in preventable diseases like tuberculosis, pellagra, diphtheria, spotted fever, mental disorder, & especially venereal disease?

5. **Otherwise:** From Lima, Peru, comes the new **Revista de Medicina Experimental**, with C. Gutierrez-Noriega's report on the medullary vasoconstrictor center. O. H. Robertson (Science, 97: 142, 1943) says triethylene glycol is the best of all glycols for sterilizing air (1 mgm per 200 liters of air—0.1 cc. per 800 cu. ft.). J. J. Lalich & A. L. Copley (Arch. Surg., 46: 224, 1943) note that dicoumarin doesn't much decrease clot resistance in wound thrombi. Australian committee on Survey of War Medicine has excellent review on treatment of burns (Suppl. 7, Med. J. Austral., Jan., '43). H. O. Calvary & crew begin work on bacterial pyrogens (J. Amer. Pharm. Asso., 32: 65, 1943). D. Court & S. Taylor find pitressin tannate suspended in peanut oil effective on single intramuscular injection in controlling diabetes insipidus for many days, (Lancet, 1: 265, Feb. 27, '43). C. H. Rammelskamp & C. S. Keefer find penicillin absorbed & excreted mo rerapidly after intrathecal injection in meningitis patients than in healthy humans, & wish less untoward effect (Amer. J. Med. Sci., 205: 342, '43). Vale and Edgar Allen using colchicim to produce cellular mitosis to study differential growth in ovaries of rats (Amer. J. Anat., 72: 291, '43).

THE FOUR HUNDREDTH ANNIVERSARY OF THE GREATEST MEDICAL BOOK

Four hundred years ago was just about as turbulent a time in Europe as now. The Reformation was on, and religious warfare and persecution was at its bitter beginning. Basle, at the juncture of the cultures of the Rhineland, France, and Italy, was a bustling, hustling city. Here worked the great humanist and printer, Oporinus.

For many months he had been associated with a brilliant young Flemish teacher in Padau, Andreas Vesalius. Vesalius had been born in Brussels only twenty-seven years before. But he had already stirred violent argument about his medical ideas. He had studied in Paris, but found that his teachers knew less about the human body than he knew, as a result of his own observations. As a youngster he had already examined the bodies of all sorts of insects, fish, birds, and animals. His curiosity now aroused, he began to steal the bodies of executed criminals for dissection—a dangerous and criminal undertaking in itself. Unfortunately, this was the only way in which he could obtain dissecting material.

He found that even the revered authorities, Galen, Aristotle, Mundinus, Avicenna, did not know how the human body was built—although their ideas on the matter had been piously taught and believed for centuries. The young University at Padua, near Venice, employed Vesalius as a teacher in its new Medical School. Vesalius saw his chance.

How hard he worked, we don't know, but we may guess by the grandeur of his results. Obtaining the help of the best artist available, Jan van Calcar, Vesalius dissected carefully, and Calcar drew what Vesalius revealed. Somehow, Vesalius got the drawings and his descriptive account to Basle for the great printer Oporinus to examine.

Oporinus recognized the value of the work. A trial publication, with a few wood-cuts for illustration, showed that medical students wanted to learn more than their teachers could give them. Accordingly, Oporinus devised the most beautiful book he could, for the publishing of Vesalius' ideas, and of Calcar's beautiful drawings. These were transferred to wood-blocks with such remarkable skill that they

are still in existence (unless the Nazis have destroyed them). The book was published in 1543, with superb care—and in sumptuous folio style. Each chapter began with a delightfully appropriate initial letter cut in wood and showing little cherubs in various dissecting room operations. The paper was the finest obtainable, and the typography was excellent.

Then a peculiar thing happened. Everyone who thought it necessary to appear up to the minute in medicine bought a copy—but apparently didn't use it. The book was too big, and too good. Besides, it wasn't practical. It described in brilliant essay form the fabric or structure of the human body—but it didn't help one in dissecting, or in memorizing how the body was put together. So scholars treasured the book along with collectors, but doctors and students didn't use it.

The result is that now first edition copies are usually seen in fresh almost unused condition. In 1555 a second edition was published even more sumptuously by Oporinus. Perhaps it paid him. In 1568 a third edition appeared in Venice, with newly cut illustrations, and in smaller size. Then gradually surgeons, like the great Ambrose Pare, learned the value of Vesalius' work. Imitators copied the illustrations and ideas, condensing them so that they could more easily be learned. Soon it was realized that Vesalius had indeed laid the foundation for modern anatomy and surgery. But that was many years after he had been dead, disappointed at the utter lack of appreciation which he had so eagerly anticipated as a young man when his great book first appeared.

The late Harvey Cushing devoted many years of his life to the preparation of a bio-bibliography of Vesalius, which he hoped to have completed in this anniversary year of the publication of the *Fabrica*. His friend Doctor John F. Fulton at Yale is planning to issue this important study as soon as possible. The importance of the *Fabrica* is indicated by the fact that the Cushing check list notes ninety-one editions and modified versions from the sixteenth to the twentieth century.

TO PHYSICIANS OF THE STATE OF TEXAS,
OFFICERS OF COUNTY MEDICAL SOCIETIES,
COUNTY JUDGES AND RELIEF AGENCIES:

March 16, 1943.

The Clinic of the University of Texas School of Medicine and the John Sealy Hospital desires and is prepared to receive indigent and part-pay patients from the entire State of Texas for the primary purpose of providing additional and diversified clinical material for teaching purposes. Incidentally, this will serve the additional purposes of assisting in the care of the indigent sick of the state, and in some instances, of offering physicians a diagnostic service for certain of the more difficult cases who cannot afford private consultation. These patients will be received at the Clinic and into the Hospital under the following conditions:

1. Applicants for admission must be residents of Texas.
2. Patients must be seen and referred to the Clinic by a licensed physician of the State of Texas.
3. An application form is to be filled out by the referring physician.
4. *Patients will be received at the Clinic and Hospital BY APPOINTMENT ONLY.*
5. In the event of an emergency, appointments may be requested and granted by telephone or telegram, preferably the latter.
6. Application for admission to the Clinic will be received and accepted on the basis of need on the part of the patient and suitability for teaching.
7. The Medical School of the University of Texas and John Sealy Hospital assume no responsibility for transportation to or from the Clinic and Hospital.
8. The Medical School of the University of Texas and John Sealy Hospital accept no responsibility for the maintenance of the patient while in Galveston unless the patient is admitted to the Hospital.
9. The Medical School and the John Sealy Hospital must retain complete authority and responsibility for admission to the Hospital.

10. Patients will be admitted to the Hospital on the basis of need of hospitalization, suitability for teaching, and availability of beds.

11. The following types of patients will be received at both the Clinic and Hospital:

a. Strictly indigent:

(1) Upon proper certification of the medical indigency of the patient by the referring physician and certain local authorities, such as the county judge, this type of patient will be received at the Clinic and in the Hospital, when necessary, without cost for any service to the patient.

b. Part-pay:

(1) One type of part-pay patient will be received upon proper certification by the referring physician, with the understanding that the patient will pay a nominal sum of two dollars for registration, half the usual private rates for various types of laboratory work, such as clinical, x-ray, and electrocardiographic work, and unusual types of medication, and on a cost basis of $3.50 per day for hospitalization in the Wards of the Hospital. They will not be required to pay professional fees for attending physicians. They will be used for teaching purposes.

(2) Another type of part-pay patient will be received in the Clinic and Hospital upon proper certification by the referring physician. This classification is designed to include those patients who are not indigent but who are not able to pay as much as those classified under Part-pay: (1). These patients will be required to pay a nominal registration fee of one dollar, one-fourth of the usual private rates for all laboratory services, such as x-ray, clinical laboratory and electrocardiographic work, and $1.75 per day for hospitalization in the Wards of the Hospital. They will not pay any professional fees. They will be used for teaching purposes.

DIRECT ALL APPLICATIONS AND INQUIRIES, BY LETTER, TELEPHONE OR TELEGRAM, TO THE DIAGNOSTIC CLINIC, UNIVERSITY OF TEXAS SCHOOL OF MEDCINE AND THE JOHN SEALY HOSPITAL, GALVESTON, TEXAS.

Your cooperation is cordially requested in developing this service in a helpful manner to all concerned.

RAYMOND GREGORY, M. D.
Director of the Out-Patient Clinic.

CLINICAL OBSERVATIONS ON SPOTTED FEVER IN THE GULF COAST AREA OF TEXAS

BOYD READING AND HUGO A. KLINT*

In extensive areas of Texas, Louisiana, Florida, and the southeastern Atlantic states, *Amblyomma americanum* is the most common tick indigenous to these regions. Recent tick surveys made by Anigstein and Bader (1); Kohls and McGregor (5) in the region of West Columbia, Texas, Braozria County, following an outbreak of spotted fever in this locality revealed that in about six thousand ticks collected *Amblyomma americanum* were the only ticks found.

CASE REPORTS

Case I

G. C., aged five years, female, resident of Alvin, Texas, Brazoria County, was admitted to the hospital June 8, 1937, and died June 15, 1937.

This child entered the hospital with the complaint of fever and vomiting. The illness began on June 3, 1937, with a sudden elevation of temperature. This was associated with vomiting. She had complained bitterly of pain over the body for three days prior to admission to the hospital. This pain had prevented her from sleeping. In addition, since the onset of the illness, the patient had been delirious on several occasions.

There was no history of tick bites, nor was there a tick found upon the patient upon admission to the hospital. The past history and family history were inconsequential.

Examination of the patient revealed a child obviously very ill. The temperature was 105° F; pulse 150 per minute; respiration 30 per minute. During the illness the temperature ranged between 99° and 106° F. The pulse continued at a level of 150 per minute. The patient was dehydrated. The throat was hyperemic. The lungs were clear. Aside from a rapid heart rate, no other abnormalities were noted in the cardio-vascular system. The abdomen was tender to palpation. The liver and spleen were not palpable. There was a slight muchal rigidity. The child was delirious. There was an acute catarrhal otitis media involving the right ear. There was a petechial rash over the entire body, particularly the extremities and the trunk. The rash was present also on the face. The tourniquet test was positive. The palms and soles were not mentioned in the examination. The child died on the twelfth day of the disease.

LABORATORY DATA: Frequent analyses of the urine revealed nothing abnormal. The red blood cell count averaged 3,500,000. The

* From the Department of Pediatrics, Medical Branch, University of Texas, Galveston, Texas. Received for Publication February 16, 1943.

white blood cells ranged between 10,000 and 20,000. The hemoglobin values ranged between 69 and 78%. Filaments 40%; non-filaments 60%. Platelets 48,000. Bleeding time 4 minutes, 30 seconds; coagulation time 3 minutes, 20 seconds. The granular cells varied between 92 and 98%. The blood Wassermann was negative. Two examinations of the spinal fluid made at intervals of 24 hours were entirely negative. Blood obtained on the 11th day of the illness gave a positive agglutination in a dilution of 1:320 for Proteus X_{19}.

Agglutinations were negative for typhoid, paratyphoid, undulant fever, and tularemia. The blood cultures were consistently negative. The clot retraction was normal.

The findings at necropsy included acute myocarditis, congestion of lungs. The spleen weighed 130 gms. It was purplish red in color and histologically revealed acute splenitis. Meningeal congestion with cerebral congestion and edema was found.

A recent re-examination of the tissues by Anigstein and Bader revealed rickettsial bodies similar in appearance to the rickettsiae found in cases III and IV.

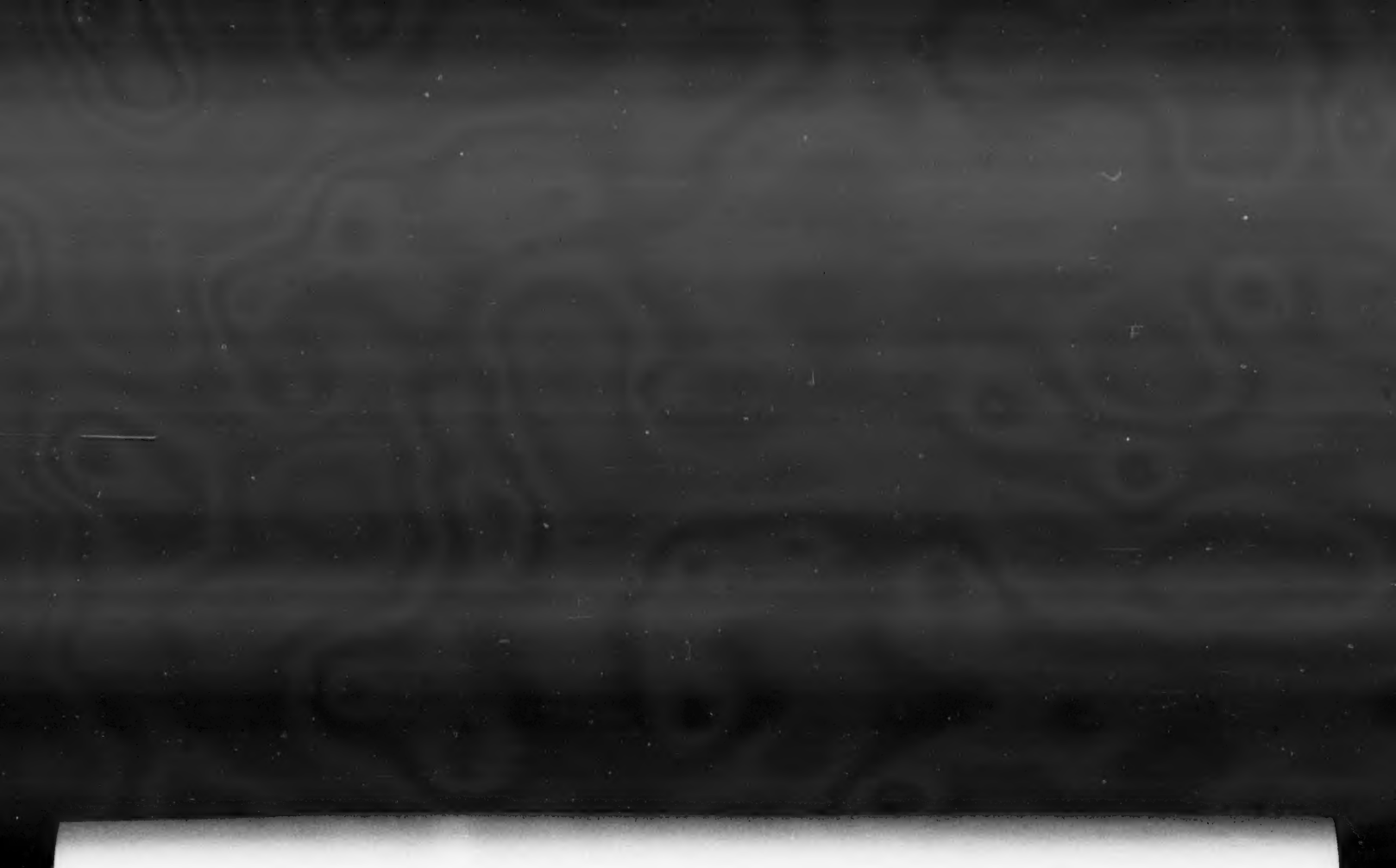
Case II

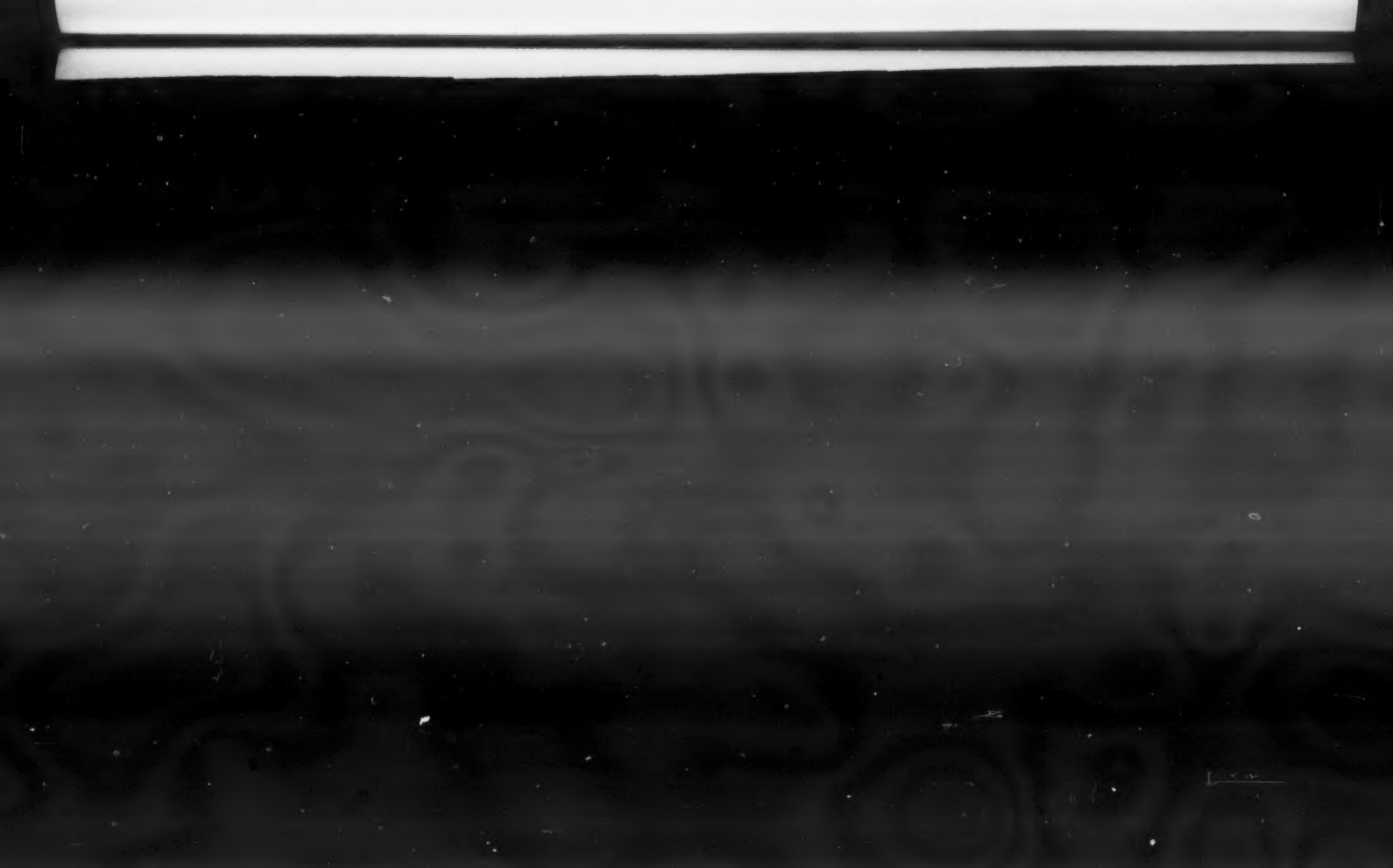
K. F. H., aged seven years, female, resident of Alvin, Texas, Brazoria County. Admitted to the hospital July 23, 1939, and died August 13, 1939.

This patient was admitted to the hospital with the chief complaint of fever and rash. The onset of the disease was sudden with chills, fever, prostration and weakness. Irritability was a very early symptom and from almost the very beginning the child complained of an achingness or soreness over the body. The onset of the disease was July 15, 1939. The following day the lymph nodes of the neck were swollen and a tick was found on the back of the neck at the hairline which was identified as Dermacentor variabilis (2). A rash soon appeared on the extremities, arms, and legs, and upon the face. At first this was a macular type of eruption but it soon became petechial and covered the entire body.

Eventually these lesions became coalescent and definite ecchymotic. Because of photophobia which was a marked symptom at the onset of the illness and due to the macular type of eruption, it was thought that measles was the cause of the symptoms. The photophobia was marked. No Koplik's spots were present on the buccal mucous membranes. In addition, the child had intense manifestation of hyperasthesia. The slightest touch to the skin caused untold pain and discomfort. She could not bear the weight of bed clothing without bitterly complaining. She also complained of pain in the right elbow joint; she was unable to fully extend the right elbow. The child had always been healthy previous to the present illness. She had lived in Brazoria County, Texas, all of her life and had not been out of that community at any recent time.

Physical examination of the child revealed the patient to be acutely ill. She kept her eyes closed most of the time because of photophobia. A very faint hemorrhagic rash was present on the face





Pictures of the four patients described.

but was much more marked and much more extensive on the trunk and the extremities. The palms and soles were also involved in this eruption. In certain areas coalescence of the rash had occurred and definite ecchymotic areas were present. The pulse rate was rapid; no heart murmurs were audible. The temperature upon admission was 105° F. The temperature curve was irregular, ranging between 102° to 106°, with remissions of several degrees. The pulse rate ranged between 130 and 150 continuously. The hyperasthesia of the abdominal wall made examination difficult. The child complained of tenderness of the masseter muscle, because of this she had some difficulty in opening and closing the mouth.

LABORATORY DATA: Frequent examinations of the urine revealed a trace of albumin, occasional granular casts, no blood, and occasional pus cells. Hemoglobin value ranged between levels of 73 and 85%. The red cell count varied between 3,600,000 and 4,100,000. Leucocytes ranged between 7,000 and 18,000. At all times a polynucleosis existed, varying from 70 to 80%. The cells were of the mature type. Filament forms comprising 62 to 70% and non-filament forms 5 to 15%. Agglutination tests: On July 22, 1939, the Widal test was negative. Agglutinations for Para Typhoid A and B were negative. The Weil-Felix test was negative and the agglutination test for bacillus abortus was negative. A lumbar puncture was done, the examination of the spinal fluid was entirely negative. The Weil-Felix test was repeated on July 31, 1939, and was positive in a dilution of 1:320.

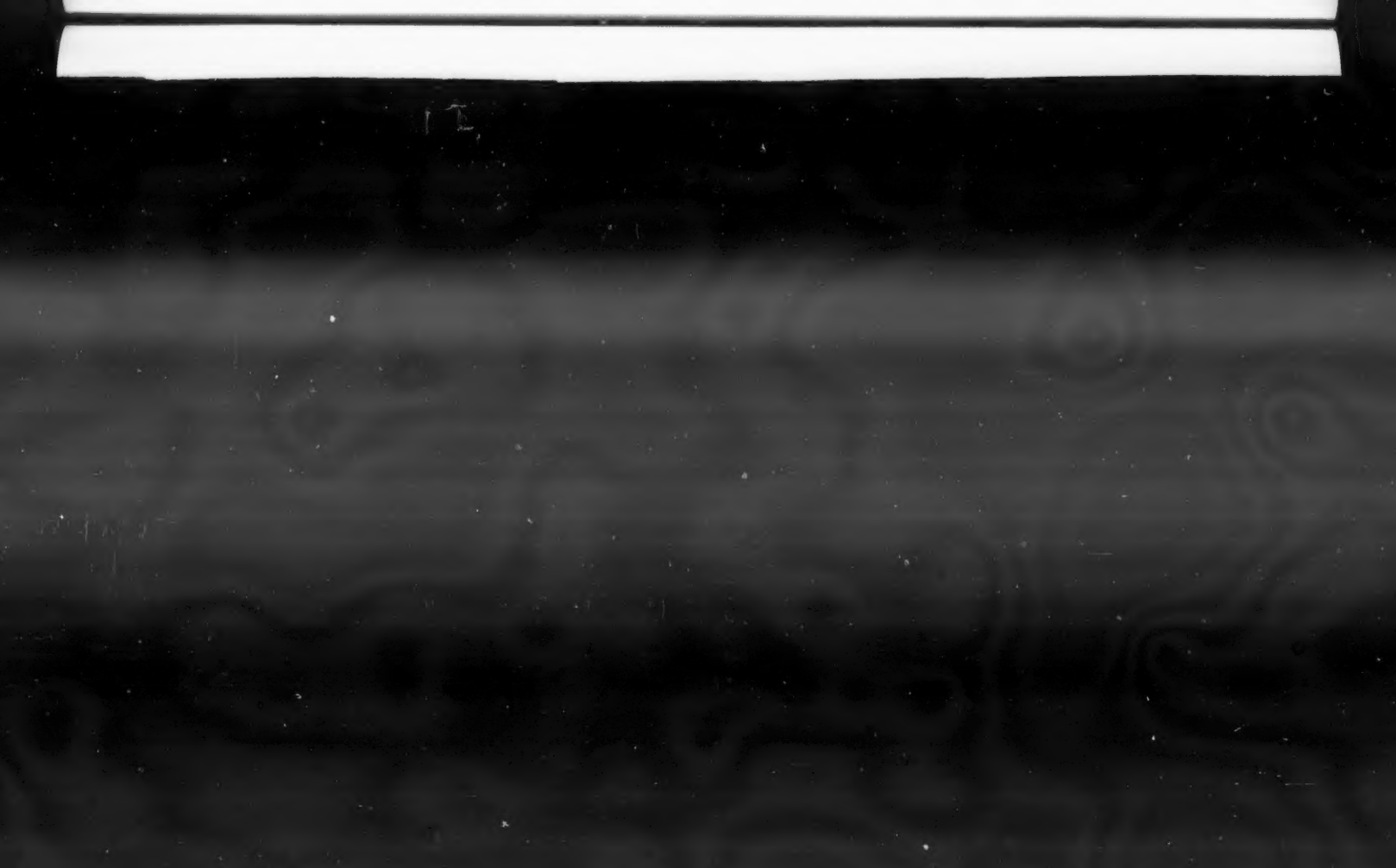
COURSE OF DISEASE: Marked delirium was present during the entire course of the disease. During this period the temperature remained high. On the nineteenth day of the disease definite signs of pneumonia were found in the right lung. X-ray examination revealed dense consolidation of the upper two-thirds of the right lung. Death occurred on the 21st day of the illness. No necropsy was obtained.

Case III

S. E. D., aged three years, male, resident of West Columbia, Texas, Brazoria County. Admitted to the hospital June 18, 1942, and died June 23, 1942.

This child was admitted because of fever and rash. The parents were well. The mother was twenty-three years of age and the father was thirty years of age.

Two other children were living and well, aged four and six years respectively. One girl at the time of this history was ill supposedly with measles, that is, she had a maculo-papular eruption although the parents stated that the child had had measles at a previous time. This girl, aged ten months, is Case IV in this series. The patient had always been healthy. There was nothing abnormal in the birth history, the feeding history, nor the developmental history. The child's health had always been good. In 1941, he had an attack of measles. He was in bed for ten days, recovery was complete. He was vaccinated against smallpox in 1941, and was immunized against diphtheria in the same year. A tuberculin test done in October, 1941, which was negative.



PRESENT ILLNESS: The child was perfectly well until June 14, 1942, at which time he suddenly developed fever. This was quickly followed by a macular eruption which appeared first on the back and then spread to all parts of the body except the face. The following day vomiting occurred which continued until June 16, 1942. During this time the child complained of a sore throat. A physician was consulted and he confirmed the throat inflammation. No explanation was given, however, for the rash. June 16, 1942, the child became irritable and apparently seemed chilly although an actual chill was not described by the parents. The vomiting had become less severe. On June 16, 1942, he had a generalized convulsion which lasted for ten minutes. A second convulsion occurred during the afternoon of June 16th. The family lived in a trailer camp at West Columbia, Texas, Brazoria County, near a small creek. Previous to this they had lived in Bay City, Texas. Their drinking water was obtained from a well. The milk which the children drank was pasteurized. The family had no pets.

The mother stated that many ticks were picked from the bodies of the children at various times, especially from the arm pits, groins, and head. Two other children in a different family were taken with similar symptoms, that is, rash, fever, vomiting. These children were treated by a local physician and made a complete recovery.

Physical examination revealed the patient to be acutely ill. Temperature 104° F; respiration 40; pulse 160. The child appeared to be lethargic, the cheeks were flushed, and the skin over the neck, chest, and forearms was covered with small pin-point petechial hemorrhages. The conjunctivae were injected. The pupils reacted to light and accommodation. The nose and ears were normal. Few petechial hemorrhages were noted on the mucous membrane of the mouth and gums, none were seen on the hard or soft palate. The throat was moderately hyperemic. The lymph nodes of the neck were moderately enlarged. Thre was no nuchal rigidity. The heart and lungs were normal. The abdomen was moderately distended. The liver and spleen were not palpable. The petechial eruption was noted on the palms and soles. The following day the rash had become much more confluent. There were large hemorrhagic areas distributed over the skin surface over the entire body. This increased from day to day, until towards the end of the illness these areas had become tremendously confluent. Photograph 1 and 2 will illustrate these points. Just before death necrotic areas over the buttocks, at the end of the penis, and on the scrotum developed. These areas were all at point of skin contact. The spleen became enlarged shortly before death.

LABORATORY DATA: Urine analysis: Specific gravity 1.005; reaction acid; albumin grade I; sugar negative; few finely granular casts, some coarse granular casts; six leucocytes per high power field were found.

The red blood count ranged between 3,400,000 and 4,000,000; the white blood cells ranged between 3,900 and 15,500. The hemoglobin value varied between 9.5 grams and 11.38 grams. The polynuclears

varied between 73 and 93%; the lymphocytes between 24 and 6%. The platelets numbered 24,000. The clotting time was 3 minutes. The blood Wassermann was negative. All blood cultures were negative. The following agglutination tests done on the sixth day of the disease were negative: Typhoid O and H; Paratyphoid A and B; Proteus X_{19} and Bacillus Abortus. The temperature ranged between 100-105° F.

NECROPSY: The gross pathology revealed hemorrhages in most of the organs. The spleen was enlarged and very dark in color. Histologically, the blood vessels showed endothelial proliferation and perivascular infiltration. Intracellular rickettsiae were found by Anigstein and Bader (1) in the endothelial cells of most of the organs. Immunity tests (1) proved that guinea-pigs inoculated with blood from this patient remained immune from known strains of Rocky Mountain Spotted Fever strains.

Case IV

A. L. D., ten months, female, resident of West Columbia, Texas, Brazoria County. Admitted to the hospital June 20, 1942, and died June 23, 1942.

This patient is the sister of S. E. D., Case III. She was admitted to the hospital with the same symptoms as her brother, that is, fever and rash. She became ill on June 15, 1942, one day following the onset of the illness of her brother. She developed a macular rash which appeared first on the hips and gradually spread to the entire body. The local physician made a diagnosis of measles, however, there was no photophobia nor Koplik's spots. The fever began suddenly the day before the appearance of the rash. Upon admission to the hospital on June 20, 1942, the skin was covered with a hemorrhagic eruption similar to that present on the body of her brother. The eruption was at first petechial and then became diffusely hemorrhagic. It involved the extremities, body, face, palms, and soles. Pressure necrosis developed on anterior chest wall and chin. (Photos 3 and 4). Petechial hemorrhages were present on the mucous membranes of the mouth and on the soles and palms. The fever ranged between 103 and 106° F. The course of the illness was identical with that of her brother. A complete necropsy was obtained and animal inoculations were made from the body tissues as well as from the blood of the child before death. The results were identical with those of Case III.

LABORATORY DATA: Many ticks had been removed from this child at various times. Examinations of the urine were negative except for occasional granular casts. A trace of albumin was present in most specimens examined. Erythrocyte counts varied between 2,400,000 and 4,000,000. The leucocytes ranged between 2,800 and 4,600. Hemoglobin value varied between 45 and 83%. The polymorphonuclears ranged between 60 and 69% and the lymphocytes between 30 and 35%. The platelets numbered 148,000; the clotting time was 3 minutes and 6 seconds. The blood Wassermann was negative. All the agglutination tests were negative. Blood cultures of the stool and urine were negative. A few days before death the spleen of this child became considerably enlarged.

COMMENT

A review of the literature reveals that only one, or possibly two proven cases of spotted fever have been reported which originated in Texas, although a number of doubtful cases have been reported to the Texas State Department of Health and to the Rocky Mountain Spotted Fever Laboratory at Hamilton, Montana. In most instance confirmation of the diagnoses has been lacking. The only case of spotted fever originating in Texas and confirmed by complete immunity studies was that reported by Kemp and Grisby (3). Another case was reported by McDaniel (4) but the diagnosis was not substantiated by animal inoculation nor cross immunity tests.

Because of the increasing number of cases of endemic typhus fever which are being reported from this locality, we wonder whether or not some of these cases of reported typhus fever are in reality cases of spotted fever. Case I in this report was originally diagnosed as a case of typhus fever, yet many of its features resemble more closely those of spotted fever.

The second interesting point with regard to these four patients is the fact that they all came from the same locality, that is, Brazoria County, Texas, and lived within a few miles of each other. A thorough survey was made of the trailer camp, the other inhabitants of the camp, and members of the patient's family. In no instance was any tick found except *Amblyoma americanum* in the immediate surroundings. Because of this fact and because of the surveys for tick collection previously mentioned in which only *Amblyoma americanum* were found, it becomes interesting to speculate as to whether this is perhaps a vector of spotted fever. The circumstantial evidence speaks strongly in favor of this belief. Conclusive evidence is lacking to support the conviction that Case I was spotted fever, however, Cases III and IV are proven and in Case II the diagnosis of spotted fever is in all probability correct.

The Sao Paulo type of spotted fever described by Lemos Monteiro (1931) has many points of similarity to the type of spotted fever found in this section of the Gulf Coast. The

rickettsial bodies found in the South American type of spotted fever are similar to those found in the cases reported in the Gulf Coast area.

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INVESTIGATIONS ON RICKETTSIAL DISEASES IN TEXAS

PART I. EPIDEMIOLOGICAL ROLE OF TICKS COMMON TO THE GULF COAST IN RELATION TO LOCAL SPOTTED FEVER.*

LUDWIK ANIGSTEIN AND MADERO N. BADER

The great variety of physiographic conditions of the immense areas of Texas and the manifold fauna and flora influenced by all climatic zones offer a wide range of epidemiological possibilities, particularly to diseases transmitted by arthropods. The investigator has, therefore, in Texas an almost ideal field to study the mode of transmission of such diseases as tick-borne rickettsioses, for which the local epizootological factors are responsible. It is particularly the subtropical Gulf Coast area, the habitat of a great variety of ticks, where the zoogeographical conditions open wide potentialities of tick transmission. These circumstances create the possibility that various tick genera, as well as their vertebrate hosts, might be involved in the epidemiology of local spotted fever.

The above conception is not entirely new, as Parker, Philip and Jellison (1933), recognizing the wide distribution of spotted fever throughout the country have considered the "potentialities of tick transmission in relation to geographical occurrence in the United States." On the basis of laboratory transmission tests with various ticks collected from different parts of the states and then experimentally infected with spotted fever the above authors concluded that "in all sections of the United States there are ticks that are actual or potential carriers of the virus."

In pursuing our researches we were interested in knowing whether the most prevalent ticks in the Gulf Coast of Texas are actual carriers of pathogenic rickettsiae in nature and, particularly, to investigate the epidemiological relationship of these ticks to spotted fever. Experimental

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transmission tests of the infection have been omitted inasmuch as the same genera and species of ticks have already been tested by the above mentioned authors.

Parallel to this method of attack, a large scale serological survey of domestic animals (dogs, cattle, and hogs) was carried out. The purpose of this survey was to obtain a cross-section of Weil-Felix reactions as response to spontaneous rickettsial infection in those animals which come in contact with man.

Finally, the authors had the opportunity to study an outbreak of spotted fever which has occurred in the Gulf Coast and to correlate their epidemiological observations with the present findings. (See part 2.)

SEROLOGICAL SURVEY:

Dogs of various origin from Galveston, as well as from the mainland, have been examined for ticks and their sera tested by the Weil-Felix reaction against three strains of Proteus X:OX_{19}, OX_2, OXK. Out of the total of 98 dogs sera, 29 gave a positive Weil-Felix, in most cases with all three strains, from 1/80 to 1/160 and one serum was positive up to 1/320, i. e. 30 per cent. This series includes 21 dogs heavily infested with the tick *Rhipicephalus sanguineus*. The latter group gave a positive WF in 19 cases, i. e., 94.7 per cent. (See footnote, p. 114.) These striking differences gave reason to suspect the possibility of the dog and the brown dog tick *(Rhipicephalus sanguineus)* playing a role in the epidemiology of local rickettsiosis. The part of the dog as natural reservoir of "fievre boutonneuse" transmitted by *Rhipicephalus sanguineus* has been established by Durand (1932). It has also been proven that the same tick is the vector of "tropical typhus" in Kenya (Roberts, 1935). In the Western Hemisphere the dog has been found reservoir of the "Sao Paulo typhus" in Brazil by Dias (1937) and Travassos (1938), the vectors being the ticks *Amblyomma striatum* and *A. cayennense*. The possibility of the active role of *R. sanguineus* in the epidemiology of Rocky Mountain spotted fever has been considered by Parker, Philips and Jellison (1933) who found that under laboratory conditions this tick is a very efficient transmitting agent and that there is reason to believe that it may become a natural agent in spotted fever

transmission. These authors have also demonstrated that *R. sanguineus* will acquire infection from dogs experimentally infected with RMSF virus. It has to be mentioned that the only response of the dog inoculated with spotted fever, fievre boutonneuse, louse-borne typhus and murine typhus is the Weil-Felix reaction, otherwise the infection is symptomless (Badger, 1933; Durand, 1932; Combiesco, 1934).

The serological survey made in Rumania (Combiesco, 1934) in an area endemic for "fievre boutonneuse" revealed in 30 per cent of the dogs a positive Weil-Felix reaction, the lowest diagnostic titre being accepted 1/50. The same proportion of positive Weil-Felix tests with dog sera was found in the present studies.

The serological results of the above mentioned authors were considered as sufficient evidence to recognize the dog as a link in the epidemiological chain of the respective rickettsial diseases. In applying the same criteria to our own problem, we may conclude that the results of the present serological survey also speak strongly in favor of a similar possibility.

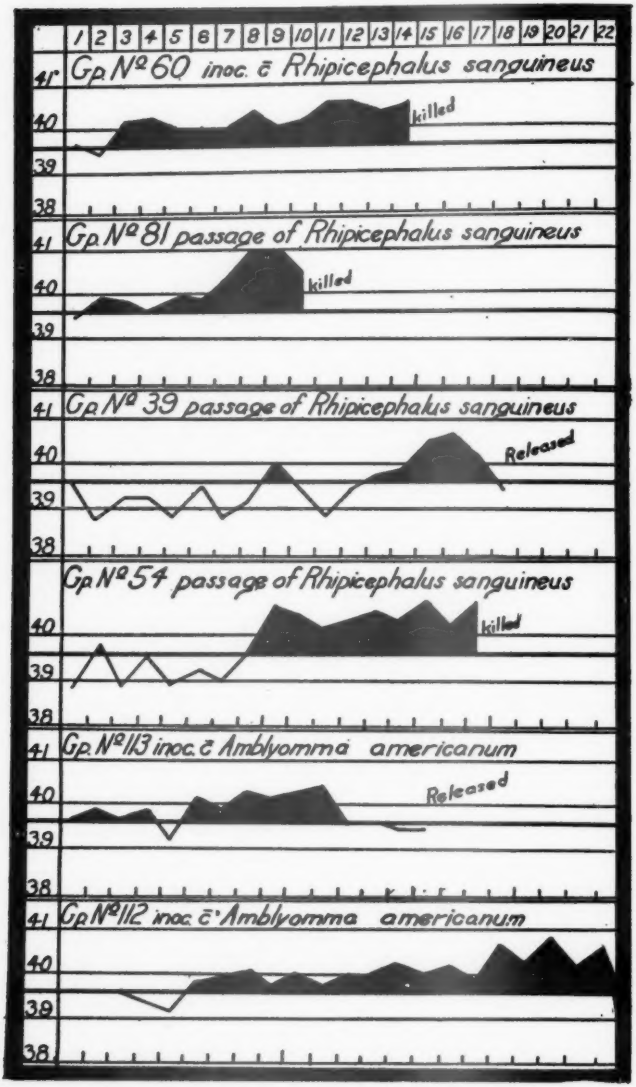
The next series of serological tests were done on cows. A total of 85 cows from the mainland includes a group of seven cows kept for experimental purposes by the Agricultural and Mechanical College Anaplasmosis research laboratory in Angleton, Texas. Because of great precautions taken by the above station these cows were found tick-free. On the other hand, the majority of the remaining cows were found infested with ticks *(Amblyomma americanum* and *A. maculatum).*

The Weil-Felix with cows-sera gave the following results: Out of the 78 of the tick series, 18 sera were positive (1/80 to 1/160), i. e., 23 per cent, while of the control group, only one out of seven sera agglutinated partially (OX_{19}) to 1/80.

Similar results were obtained with sera from hogs tested by the Weil-Felix reaction. Out of 124 sera in 22 cases the agglutination was positive in titres 1/160 to 1/320, i. e., 18 per cent. The reaction in hogs was stronger in volume as compared with dog and cattle sera.*

* An infectious agent of high virulence for guinea pigs isolated from hog-lice (Haematopinus suis) was the subject of a special study.

TABLE I


1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22
Gp. Nº 60 inoc. ē Rhipicephalus sanguineus
killed
Gp. Nº 81 passage of Rhipicephalus sanguineus
killed
Gp. Nº 39 passage of Rhipicephalus sanguineus
Released
Gp. Nº 54 passage of Rhipicephalus sanguineus
killed
Gp. Nº 113 inoc. ē Amblyomma americanum
Released
Gp. Nº 112 inoc. ē Amblyomma americanum
41
40
39
38

Temperature charts of guinea pigs inoculated with ticks from dogs and cattle.

EXAMINATION OF TICKS

This chapter is an inquiry into the possible epidemiological role of various ticks collected at random from apparently healthy cattle and dogs from some sections of the Gulf Coast where spotted fever cases were reported within the last few years.

Our attention was primarily directed to the brown dog tick, *Rhipicephalus sanguineus*. Ticks collected from dogs of Galveston and various localities of the mainland where the serological survey was performed, were inoculated into guinea pigs, white rats and rabbits. About 2500 adult ticks, males and females, were collected at intervals during the tick-seasons of 1941 and 1942. They were thoroughly washed with saline, divided into batches, ground up, and finally inoculated intraperitoneally or subcutaneously into series of guinea pigs. In addition to that about 2000 larvae and nymphs hatched from deposited eggs also served as inoculum. The majority of guinea pigs reacted with fever after an incubation period lasting from two to eleven days; the most frequent incubation was four or five days. The fever noted was of various types—abrupt elevations ranging between 40° and 41° C, or lower irregular fevers (see charts). In some other cases a rather prolonged subfebrile type was observed lasting two weeks or more and then subsiding to normal. Not all batches of ticks produced a febrile reaction. In spite of a heavy suspension of inoculated ticks, some series of guinea pigs remained afebrile during three weeks observation but a conspicuous loss in body weight was noted. Subsequent passages of this series into normal guinea pigs remained negative. Gross pathology of the febrile series of guinea pigs did not show marked changes except enlarged dark purple spleen. An almost constant feature was the injection of the suprarenals which showed occasionally hemorrhages on the cut surface. The most frequent and characteristic lesions were found in the lungs; minute petechial hemorrhages were scattered over the pale pinkish surface. A congestion of lung tissue was observed in three cases out of 145 experimental guinea pigs. Bacteriological examination of blood, lungs and spleen showed no evidence of bacterial infection.

The above infection in guinea pigs originating from *Rhipicephalus sanguineus* was carried on in passages, the brain being used as inoculum. The longest series was carried in nine passages involving 94 guinea pigs. Particular attention was paid to scrotal reaction and in the 1941 series this phenomenon was definitely established in two instances. One of these guinea pigs inoculated with 2 cc. of

Photo I. Scrotal reaction of moderate degree of a guinea pig inoculated with Rhipicephalus sanguineus collected from apparently healthy dogs.

an emulsion of 50 ticks in 15 cc. of saline developed fever on the third day and simultaneously a scrotal swelling with redness of the scrotal sac and hemorrhagic spots mainly over the left testicle (photo 1). The second guinea pig of this series also showed a swelling which was less pronounced. In both cases the swelling subsided within the next two days. No organisms were found in smears of the injected and adhesive tunica viginalis.

Of two rabbits inoculated i. p. with suspensions of *Rhipicephalus sanguineus* one became sick and emaciated on the eighth day. Post-mortem of the animal killed on the twelfth day revealed pneumonitis with distinct hemorrhagic areas in the lung tissue. The microscopic picture of the lungs was very characteristic, namely, slender diplobacillary, coccoid and lanceolate, and diplococcal rickettsia-like

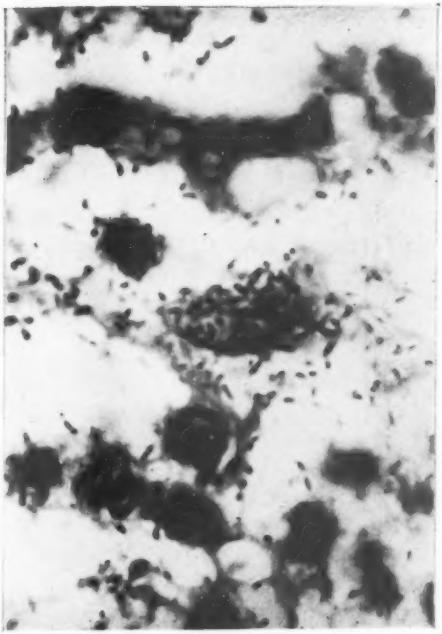


Photo II. Rickettsia-like organisms in lung section of a rabbit inoculated with Rhipicephalus sanguineus collected from apparently healthy dogs. Giemsa. 1200 X.

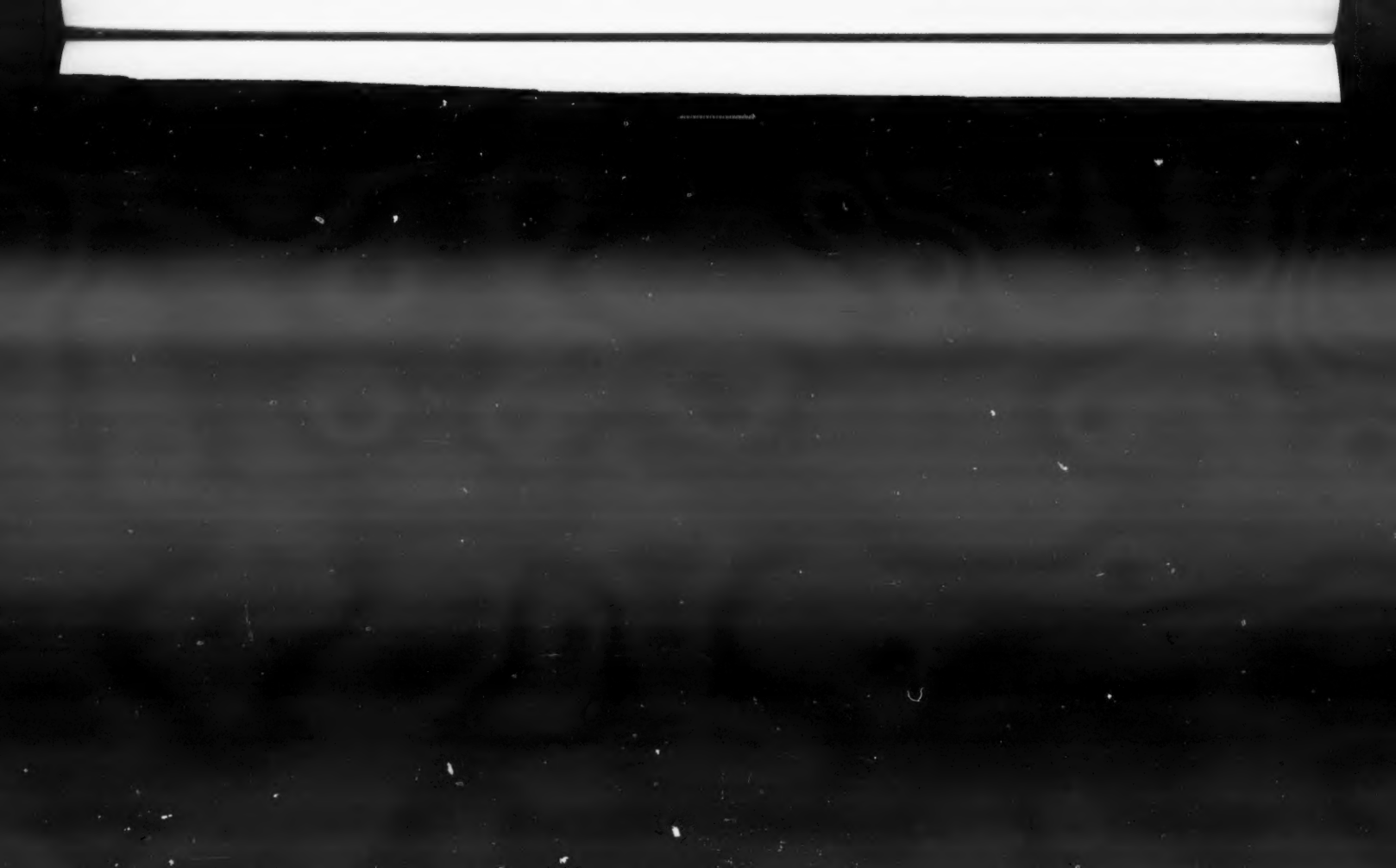
organisms invading in abundance the lung tissue. In some instances an intracellular invasion of mononuclear cells with an apparent destruction of the nucleus was noted (photo 2). It is of interest to note that this rabbit showed a rise of agglutinins against Proteus OX_{19} from 0 to 1/160 on the twelfth day after inoculation.

These experiments were taken up again in summer 1942, when the ticks were kindly supplied by Dr. H. L. van Volkenberg, College Station, Texas. A batch of 98 adult specimens of *R. sanguineus* was inoculated into four guinea pigs (two males and two females). One of the animals (No. 752) developed fever (40.1° C) on the fourth day showing a swelling and hardening of the right testicle. The scrotal skin adhesive to the testicle was purplish-red in color. The animal was killed on the sixth day after inoculation, when the fever was already subsiding. The post-mortem revealed a dark purple hemorrhagic testicle particularly on its lower pole, adhesive to the highly injected and swollen tunica vaginalis. Spleen was normal in size and appearance. In the lungs numerous minute hemorrhagic foci were found. The histopathology of testicles showed prominent vascular lesions, perivascular infiltration areas and hemorrhages. These lesions could not be distinguished from those of experimental spotted fever either from Idaho or from Texas. The lung sections showed endothelial cells filled with rickettsia-like organisms resembling those previously observed in the rabbit.

The remaining three guinea pigs of this series did not develop fever but one of them showed a scrotal reaction on the eleventh day after inoculation. The scrotum was in this case symmetrically swollen, the testicles hard, fixed, not retractible. These changes lasted for three days after which time the animal died. The other two females also died, one on the day following the inoculation, the other on the fourth day, without fever. In all these cases bacteriological tests did not show any evidence of bacterial infection.

Attempts were made to transfer the infection from guinea pig 752 in inoculating four guinea pigs with spleen emulsion. Only one of them developed fever after three days incubation, while two guinea pigs died and one remained afebrile during twelve days' observation. Further passages were unsuccessful.

The next series of experiments was carried out with *Amblyomma americanum* and *A. maculatum*. These ticks



were collected from Cleveland, Texas, and College Station, Texas. The field study in Cleveland was made in connection with recorded cases of a disease of spotted fever type and followed by a tick survey of the U. S. Public Health Service in 1939. Ticks were collected by us in that area in summer 1941 from cattle and tested on guinea pigs. The *A. americanum* inoculated intraperitoneally or subcutaneously into guinea pigs proved to be in most cases highly virulent, producing high fever of short duration following an incubation of two-three days and a high death-rate. The post-mortem revealed hemorrhages at the site of inoculation, injection of the viscera, and enlarged smooth spleen. In a few cases a fever of six to eleven days duration developed after incubation of five to six days. The dominant pathological changes were again a dark purple large spleen. The *A. maculatum*, on the other hand, was of lower virulence, but there was a definite incubation of four to six days followed by fever up to 40° C lasting for about one week. In other guinea pigs no febrile reaction was ever noticed. The post-mortem of the febrile guinea pigs showed hemorrhagic areas in the axiliary and inguinal areas with injection and swelling of the respective lymph glands, normal or moderately enlarged spleen and injected suprarenals. Lungs were in some cases congested in circumscribed areas or pale, showing petechial hemorrhages. No scrotal reaction was noticed. Bacteriological tests were negative. In further passages made with brain emulsion irregular fever was produced, and we were unable to establish the strain in guinea pigs.

In connection with the above we refer to the observations of Parker, Kohls, Cox and Davis (1939) who investigated *A. maculatum* ticks from the same place of origin. These authors reproduced in guinea pigs inoculated with *A. maculatum* a mild infection, with characteristic fever, edema and reddening of the scrotum. Cross immunity tests in guinea pigs recovered from this "maculatum fever" and reinoculated with Rocky Mountain spotted fever proved immunological identity between these two infections. Most of our guinea pigs which survived after being inoculated with ticks (Rhipicephalus and Amblyomma) were tested for immunity, but only against local strains of murine typhus. The results were negative. No strain of spotted

fever was available in our laboratory until 1942. The work is still in progress and is being now supplemented by immunity tests in relation to spotted fever.

SUMMARY AND CONCLUSIONS:

The results of the present study,* although incomplete, point to the possibility that at least two ticks, namely *Rhipicephalus sanguineus* and *Amblyomma americanum* can be incriminated as additional carriers of a spotted fever type of infection. As regards *Rhipicephalus sanguineus* a rickettsiosis was produced in a rabbit and guinea pig experimentally infected with this tick collected from apparently healthy dogs. Simultaneously, the rabbit has developed a significant rise in Proteus OX_{19} agglutinins. In addition to this, the positive results of Weil-Felix tests with dog-sera, particularly the striking differences between the tick-infested and tick-free dogs are very suggestive of *Rhipicephalus sanguineus* as source of infection and vector in nature.

Concerning *Amblyomma americanum,* we had less chance to study the effect of this tick on guinea pigs because of the high virulence of the infectious agent, but also in this series, the symptomatology and pathology of infected guinea pigs was highly suggestive of an infection of the spotted fever type.

We have less evidence in our experience with *A. maculatum* of a spontaneous rickettsial infection but judging from the above referred observations of Parker, Kohls, Cox and Davis (1939), this species has to be also considered as a possible link in the epidemiology of spotted fevers.

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*A part of the present study has been reported in a preliminary form before the Texas Branch of the Society of American Bacteriologists on May 2, 1942. (Anigstein and Bader, 1942.) The present report includes observations related to spotted fever only, which was investigated by us concurrently with the local typhus fever problem. Observations concerning the latter subject will be presented elsewhere.

Regarding *Rhipicephalus sanguineus* and *A. americanum*, both species infest man and there is reason, therefore, to include them in the epidemiological chain of spotted fever infections in addition to the previously known vectors.

ACKNOWLEDGEMENTS

The writers of this report express their gratitude to Dr. John W. Spies, then Dean, University of Texas, Medical Branch, for the generous working facilities offered by him.

The authors appreciate that their attention was called by Dr. J. T. Roberts, Assistant Professor of Medicine and Anatomy, University of Texas, Medical Branch, to the heavy tick infestation of his experimental dogs and to the possibility of their being carriers of rickettsiae.

The authors extend their gratitude to Miss Beryl Brewer, Department of Pathology, University of Texas, Medical Branch, for her valuable assistance in the preparation of the histopathological material.

Thanks are due to the Texas State Health Laboratory, Austin, Texas, particularly to Drs. S. W. Bohls and J. V. Irons, and to the Anaplasmosis Research Laboratory, Angleton, Texas, for their generous cooperation.

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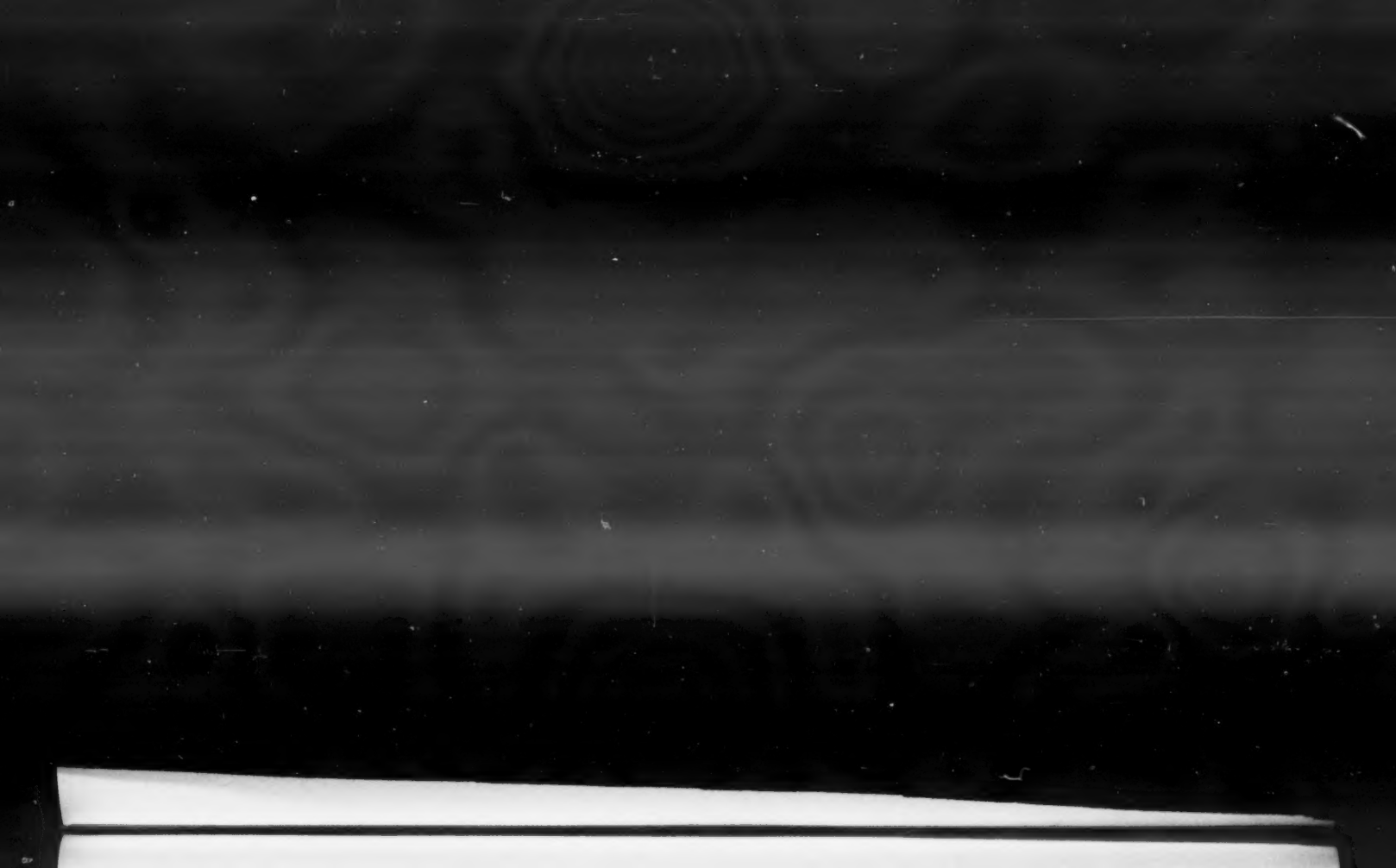


INVESTIGATIONS ON RICKETTSIAL DISEASES IN TEXAS

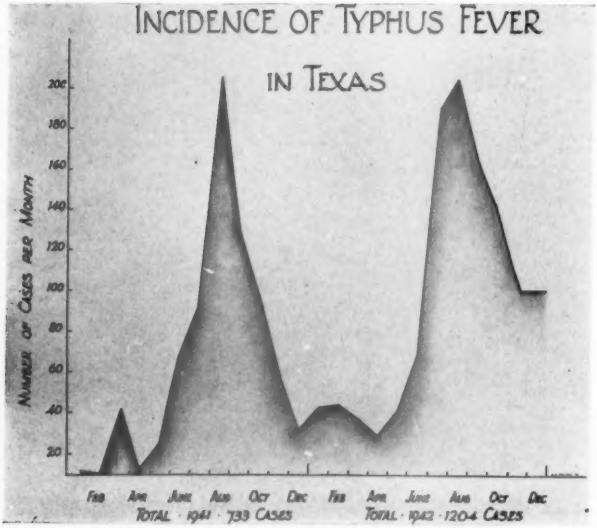
PART 2. EXPERIMENTAL AND EPIDEMIOLOGICAL STUDIES ON AN OUTBREAK OF SPOTTED FEVER IN THE GULF COAST*

LUDWIK ANIGSTEIN AND MADERO N. BADER

The State of Texas continues to be the scene of a spectacular increase in the incidence of typhus reaching in 1942 record figures in modern Texas history. The recent epidemic character of the disease, which is in marked contrast to our previous conception of its endemic nature, deserves full attention. There are also indications pointing to the enhanced virulence of the infection. It remains to be seen, however, whether the latter is actually related to typhus alone or whether it includes spotted fever as well. It is not improbable that while typical and severe cases of spotted fever have been properly diagnosed, mild ones might have been mistaken for typhus. This may partly account for the fact that only a few cases of spotted fever were reported from areas of the state where epidemiological conditions are apparently ready for a higher prevalence of the disease. According to official records there were nine cases of spotted fever reported from various sections of Texas during the decade of 1931-41. Of this series three cases were fatal but only in one of them a final confirmation of spotted fever was supplied by laboratory investigations. This conclusive evidence was offered by Kemp and Grigsby (1931) in guinea pigs inoculation with the virus from their case. No definite confirmation of the remaining cases reported as spotted fever is available. Apart from the above series, one fatal case (a child) diagnosed as typhus in 1937 in the Children's Clinic, Galveston, Texas, has been recently kindly reinvestigated at our request by Dr. R. D. Lillie, Chief, Division of Pathology, National Institute of Health, Bethesda, Maryland, who found the histopathological changes not inconsistent

* Paper read before the Annual Meeting of the American Society of Tropical Medicine, November 10-12, 1942, Richmond, Virginia. From the Department of Preventive Medicine and Public Health, University of Texas, Medical Branch.

GRAPH SHOWING REPORTED CASES OF TYPHUS FEVER IN TEXAS DURING 1941 AND 1942. NOTE THAT THE PLATEAU LEVEL BETWEEN PEAKS IS RISING.



THE STATE OF TEXAS CONTINUES TO BE THE SCENE OF A SPECTACULAR INCREASE IN THE INCIDENCE OF TYPHUS REACHING IN 1942 RECORD FIGURES IN MODERN TEXAS HISTORY. PARTICULARLY OMINOUS IS THE HIGH INCIDENCE IN THE PAST WINTER.

with spotted fever. The clinical and epidemiological data on this case are, however, strongly suggestive for spotted fever. This shows that even severe cases of spotted fever might be clinically mistaken for typhus.

The outbreak of spotted fever reported herewith occurred in the central lowland prairie of the Texas Gulf Coast, in Brazoria County. The semi-tropic climatic conditions and the fertile alluvial soil are responsible for the luxuriant flora of this area. These physiographic factors also account for a rich tick fauna, particularly abundant from May to October. The great variety of hard ticks (Ixodidae) prevalent in various sections of the Gulf Coast of Texas can be seen from the monograph of Hooker, Bishopp and Wood (1912). Dr. H. L. van Volkenberg, head of the Department of Veterinary Parasitology, Agricultural and Mechanical College of Texas, was kind enough in revising for us and bringing up to date the list of the Gulf Coast ticks which includes the following genera and species:

Amblyomma americanum
Amblyomma cayennense
Amblyomma maculatum
Boophilus annulatus
Boophilus microplus
Dermacentor halli
Dermacentor variabilis
Haemaphysalis leporis palustris
Ixodes Kingi
Ixodes scapularis
Octocentor nitens
Rhipicephalus sanguineus

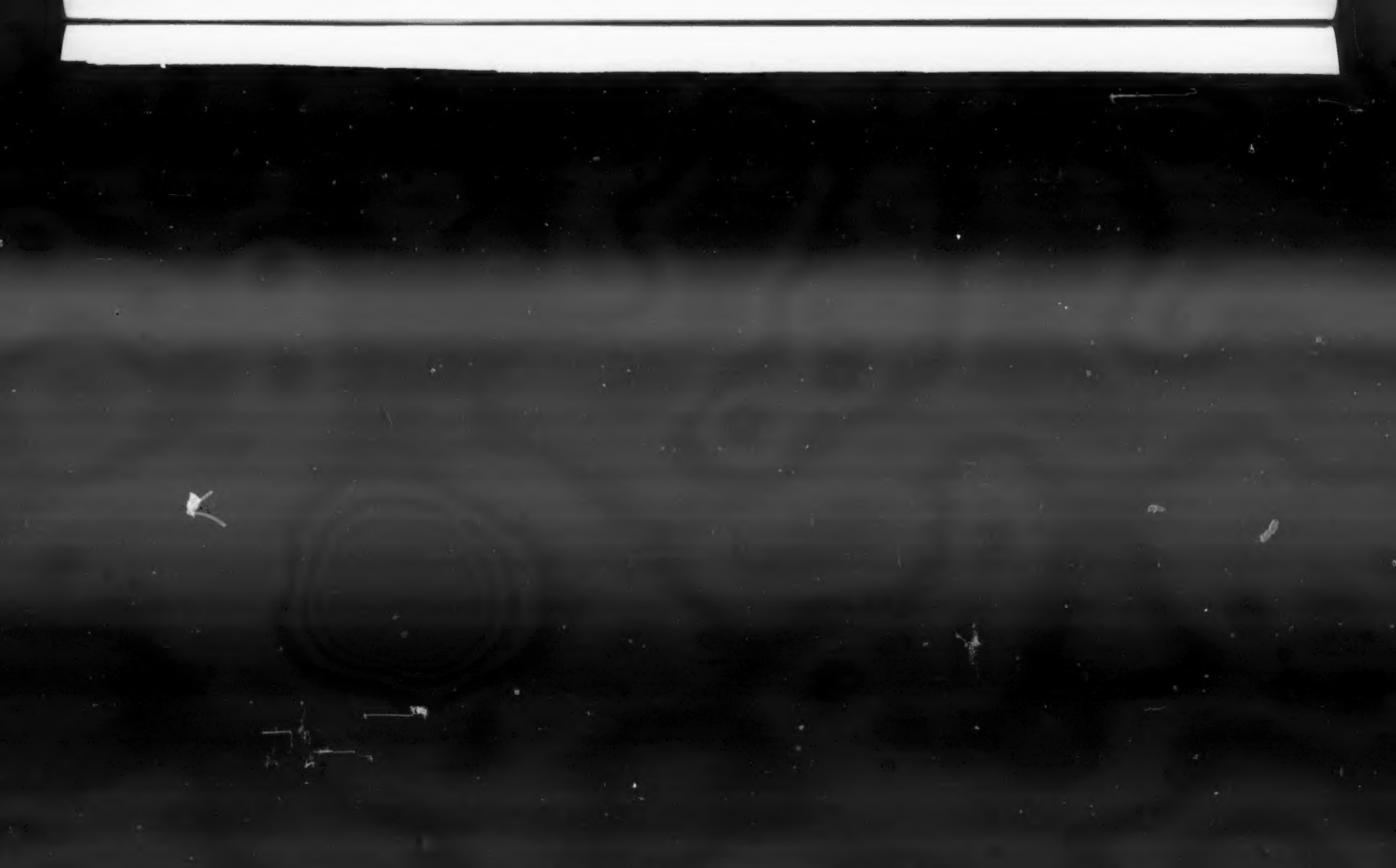
Of the above ticks only two are known as natural carriers of spotted fever, namely, *Dermacentor variabilis* and *Haemaphysalis leporis palustris.*

A trailer camp adjacent to the small community of West Columbia, at a distance of about twenty miles from the seashore, was the scene of the outbreak. The camp occupies a clearing in a heavily wooded area overgrown with brush and grass, particularly dense along a small creek draining the camp. (Photo 1.)

The main occupations of the community are rice farming and ranching. However, many workers recently came to West Columbia in connection with a chemical plant es-

1. Trailer camp in West Columbia, Texas, the scene of the outbreak of spotted fever.

tablished by the war industry in Freeport where the population is rapidly increasing. There were originally about 12 families with children living in trailers in this camp, but due to the outbreak of spotted fever only five trailers remained on the spot. Two families living in trailers a short distance apart were attacked by the disease in June, 1942. The family "B" with two children came from Louisiana in March, 1942, while the family "D" with four children came from Bay City, Texas (12 miles distant), on



June 6, 1942. Both children (a boy 3 years old, and a girl 10 months old) suddenly became ill on the 14th and 15th of June respectively, while in two "B" children the disease started on the 18th and 19th of June. In all four cases the onset of the disease was very abrupt starting with high fever, vomiting, headache, throat irritation, photophobia, and rash as described by Drs. Boyd Reading and H. Klint (This issue, page 97). Children "D," however, showed from the beginning a more severe and rather fulminant course of the disease and died in the Children's Clinic, Galveston, Texas, on the ninth and tenth day of the disease. The children of the "B" family although sick remained with their parents in the trailer camp.

The clinical symptoms of the two children (under the care of Dr. William M. Greenwood, West Columbia) of the family "B" (boys, 4 and 5 years old) were: sudden onset of high fever, vomiting, photophobia, sore throat and rash. The rash, macular in type, appeared simultaneously with fever first, around the ankles, legs and arms. It then spread over the whole body including face and palms. The rash was in one child definitely petechial with a hemorrhagic center. Both children recovered within ten days. The Weil-Felix reaction performed in one child only on the 10th day of the disease was positive up to 1/80. Both patients were frequently bitten by ticks, and prior to the disease they were playing with the "D" children in the camp, mostly on the tick infested creek area. Judging from the history and symptomatology of these two cases in which the disease began almost simultaneously with the "D" children under identical circumstances, we are justified in diagnosing the "B" cases also as spotted fever but of a milder type. The low grade of infection in the latter cases might be due to the fact that the "B" family had been in the camp four months. During that time they had been constantly exposed to tick bites at the beginning of the tick season in spring. On the other hand, the "D" children were newcomers and were attacked by ticks after their arrival when the tick season was already in full swing. It is not improbable, therefore, that the mild course of the disease in the "B" cases was, apart from the individual range of natural susceptibility, influenced by a partial immunity con-

ferred by a repeated and low phase of infectiousness of previous tick bites.

PATHOLOGY

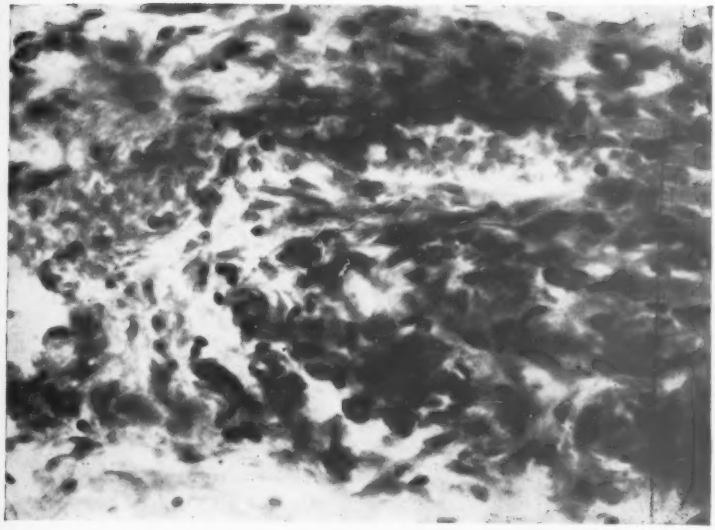
The post-mortem of the two victims "D" was performed by Dr. H. S. Sweets, pathologist, School of Medicine, University of Texas, and the following is a summary based on his report.

The skin of both children showed numerous petechial hemorrhages, some of them confluent. Superficial necrotic areas of the skin were present in both cases. Most of the organs showed petechial hemorrhages, particularly lungs, heart, kidneys. Petechiae were also found in the mucosa of the stomach and urinary bladder. An extensive hemorrhage occurred in the stomach as seen from its coffee-ground content. The pericardial, pleural and abdominal cavities in both cases contain clear, yellowish fluid. Spleen was found enlarged, dark purplish red and firm. Liver showed a purplish and yellow mottling. The tunica vaginalis of the testes was also heavily involved, showing petechial hemorrhages and clear yellowish fluid.

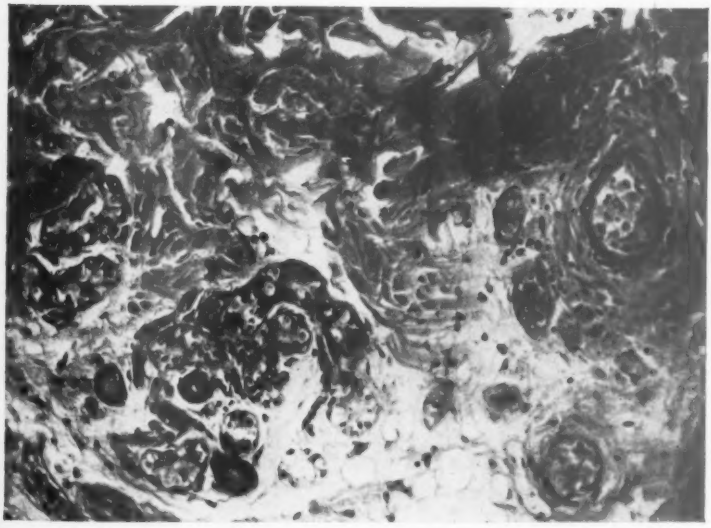
The histopathological changes were most prominent in the testes, particularly in the tunica vaginalis, where extensive hemorrhages, vascular lesions and infiltrations, mostly of endothelial origin, were noted. (Photo 2.) In the skin, scattered infiltration with groups of reactive cells composed of leucocytes and mononuclear cells are present. These cells are in places grouped around capillaries forming moderate perivascular infiltrations. (Photo 3.) There is also a marked infiltration of the connective tissues surrounding the sweat glands.

The heart shows a slight thickened pericardium and perivascular infiltration of monocytic cells. The brain shows little changes; capillaries dilated with blood and swelling of endothelium.

The above changes, although not listed in full and not prominent in all the organs, probably because of the early death, were diagnosed by Dr. H. S. Sweets and by us as suggestive for spotted fever. Some of the sections were sent to Dr. R. D. Lillie, chief pathologist, National Institute of Health, Bethesda, Maryland. According to Dr. Lillie's report, the boy's testis offers the best confirmatory evidence for spotted fever.



2. Tunica vaginalis of testis of the spotted fever case. Inflammatory foci showing hemorrhage and extensive vascular lesions. Giemsa stain. 500 x.

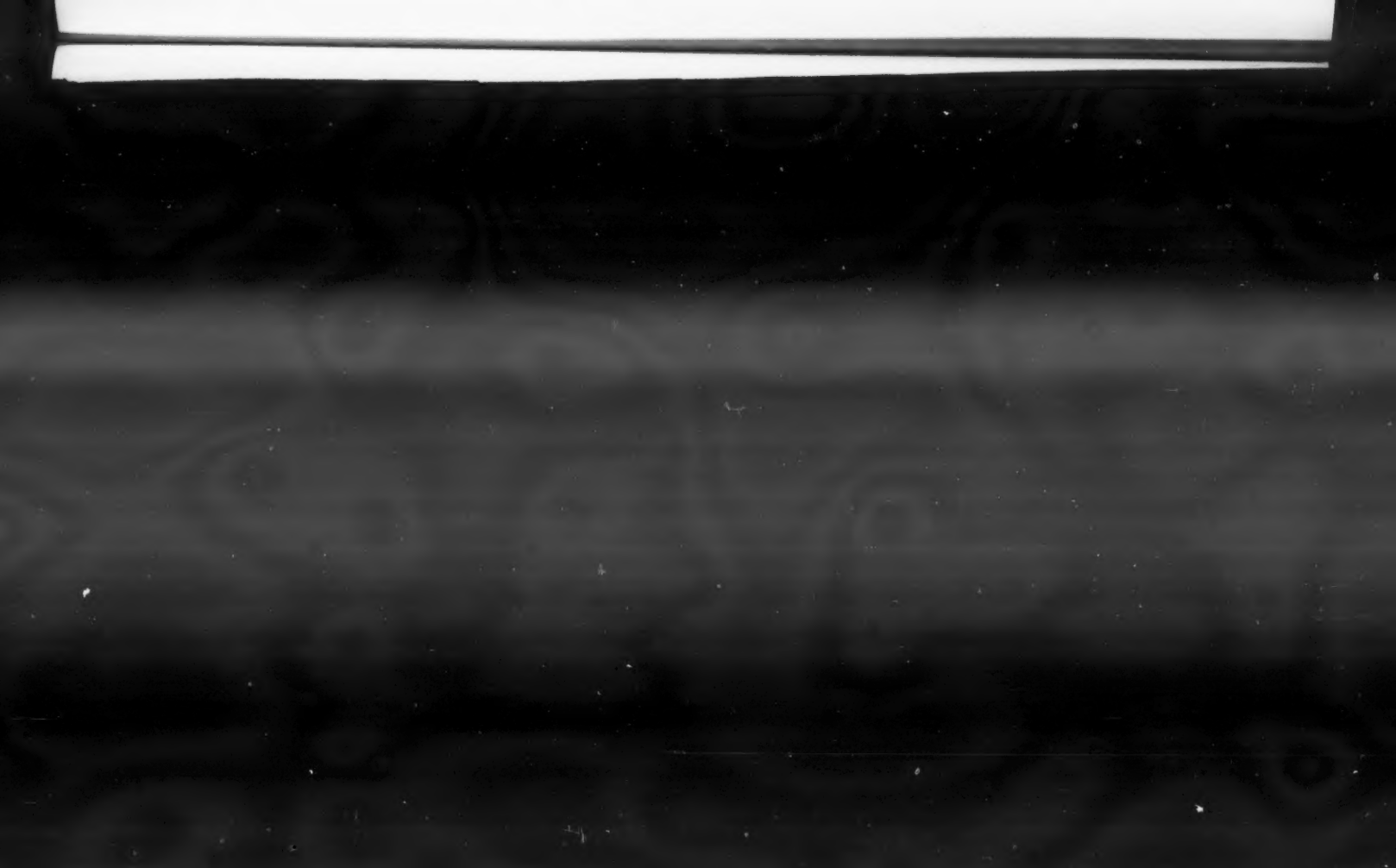


3. Subcutaneous tissue of same case showing perivascular infiltration and vascular lesions. Giemsa stain. 250 x.

EPIDEMIOLOGICAL INVESTIGATIONS.

An epidemiological study of the locality was performed by the writers of the present report on the 25th of June and the 1st of July 1942. Particular attention was paid to the area with regard to tick infestation. Simultaneously but independently from us ticks were collected from the same area by T. McGregor, entomologist, State Health Department, Austin, Texas, and Dr. W. Gingrich, Department of Bacteriology, Medical Branch, University of Texas. The most heavily tick infested section was the brush thicket alongside the creek where numerous ticks were found and identified by T. McGregor as *Amblyomma americanum*. Three dogs and one cow owned by the local residents were searched by the writers for ticks and found moderately infested with *Amblyomma americanum*.

On July 1, 1942 the second field survey was made by the writers and in that instance *A. americanum* only was revealed. After an interval of two months, at the height of the tick season, a systematic field study was repeated, this time by G. M. Kohls, entomologist from the Rocky Mountain Laboratory, U. S. Public Health Service, who was accompanied by T. McGregor. Their investigations resulted in a most abundant yield of ticks. Acording to the report kindly supplied by Dr. R. R. Parker, Director of the Rocky Mountain Laboratory, about 5500 ticks were collected, all of them being uniformly *A. americanum*. The same findings were recorded by T. McGregor as seen from the information of Dr. S. W. Bohls, Director of State Hygienic Laboratories, Austin, Texas. In all these investigations special attention was paid to the possible presence of any other ticks, particularly *Dermacentor variabilis*, but neither this tick nor any other except *A. americanum* were found in that locality at that period of time. It has to be emphasized that two specimens of ticks picked up from the mother and brother of the family "D" in June during the illness of the children were identified by G. M. Kohls as *A. americanum*. The latter fact correlated with the above findings offers, therefore, very weighty evidence that the epidemiology of the reported spotted fever cases is strictly connected with *A. americanum*.



The peculiar markings (a bright spot on the scutellum of the female) together with the abundance of this species in Texas has given it the common name "Lone Star tick." According to Hooker, Bishopp and Wood (1912) *A. americanum* has a wide range of hosts attaching to any mammal with which it comes in contact. Among domestic animals the dog is more frequently infested, cattle next. It has a wide distribution over the Eastern and Southern States and is very abundant on Texas ranches where cattle in particular suffer from heavy infestation. Man is more frequently attacked by this tick than by any other species. Experimental transmission tests made by Parker, Philip and Jellison (1933) have proven *A. americanum* an efficient carrier of spotted fever, and generation to generation transfer of the virus in this tick was established under laboratory conditions. The above authors consider *A. americanum* as the most important possible agent of human infection because of the frequent infestation of man by larvae and adult ticks of this species and its long existence as a native tick species in sections in which spotted fever now appears to be evident (l. c. 1933, 373).

According to our experience these statements apply particularly to this section of Texas. During the two tick seasons of 1941 and 1942 the writers had the opportunity to observe the extreme abundance of *A. americanum* in various counties of the Gulf Coast. Personal interviews with local inhabitants of this area (farmers, ranchers, and laborers) pointed to the familiar "Lone Star tick" as the most prevalent one, infesting man and domestic animals. Under these circumstances the *A. americanum* might be responsible for not only the maintenance and continuity of the spotted fever virus in nature but also as a carrier to man.

The above considerations are corroborated by the experimental findings in our previous studies (see this issue, p. 105). A febrile disease and pathological changes have been then reproduced by us in guinea pigs inoculated with *A. americanum*, pointing to an infection of spotted fever type. These results have been supplemented by another series of recent experiments with *A. americanum* collected from dogs and the cow found at the trailer camp. The inoculation of seven pooled adult ticks into guinea pigs produced

a febrile reaction in one of them, its partner remained afebrile and died. The febrile guinea pig was killed on the ninth day after inoculation, its brain and enlarged spleen passed to other two guinea pigs. These developed, simultaneously, a mild fever on the eighth day after inoculation, the fever lasting for three and five days respectively. Both guinea pigs were subsequently reinfected with brain and spleen emulsion of our spotted fever strain for immunity tests. As compared with two control animals there was a prolonged incubation and low fever, apparently due to partial low grade immunity. It has to be emphasized that the original tick infection in guinea pigs was mild and it is possible that due to a low phase of infectivity of ticks the immunity was incomplete. This interpretation agrees with our experience with cross-immunity tests against our original spotted fever strains in which atypical or abortive fevers conferred only a partial immunity or none.

EXPERIMENTAL DISEASE IN GUINEA PIGS

From each of the two hospital patients (AD and SD) 2 cc. of whole blood taken on the eighth and ninth day of the disease respectively (the day preceding death) were inoculated intraperitoneally into each of two pairs of guinea pigs. Two more guinea pigs were injected with spleen emulsion of the girl (three hours after death). All four guinea pigs inoculated with blood developed fever after four days incubation, while the spleen inoculation was followed by fever in one guinea pig after six days. The partner of this animal, however, remained afebrile during seventeen days' observation. Two strains of the infectious agent originating from blood of the patients later be referred to as AD and SD were established in guinea pigs by passages of spleen or brain emulsions and have reached the 25th generation. (Dec. 1942.) The average length of the incubation period is four days, as compared with an average of three days in the Rocky Mountain Spotted Fever strain kindly supplied by Dr. R. R. Parker, Hamilton, Montana, and isolated in Idaho ("Mastenbrook" strain).

The outset of the febrile reaction is in both our strains abrupt, sometimes preceded by a short drop of temperature below the normal set at 39.6° C. The height of the fever is in most cases reached on the third day, usually

exceeding 41° C and while somewhat subsiding remains still on high level for the next four-five days. The fever terminates generally by a rapid lysis, sometimes by a critical drop from one day to another and remains normal during convalescence. In some instances the course of disease was atypical: prolonged incubation followed by low, continuous or intermittent fever or the febrile reaction was absent completely. The latter condition could be interpreted either as inapparent infection or as natural immunity of those guinea pigs which proved to be immunc against a subsequent inoculation with the homologous strain. The length of fever, is as a whole, uniform in both strains, particularly in the SD strain, with variations from seven to ten days. Fever of four days duration and exceptionally long fever of twelve days have been observed in some transfer animals of the AD series. On the average the duration of fever is eight days in both strains as compared with an average of nine days for the *Dermacentor andersoni* strain in our experience. (See tables 1-4.)

The fatality rate in guinea pigs from spotted fever is as we know a character of some value in differentiating various strains. No deaths were observed in the early passages but in further transfers fatal cases occurred. There is, however, a difference between the two isolated strains as the SD strain shows up to date a 12 per cent mortality rate while from the strain AD only 5 per cent of guinea pigs died. As compared with the Idaho strain in which the mortality rate is 15 per cent the SD strain is closer related to the latter in this respect.

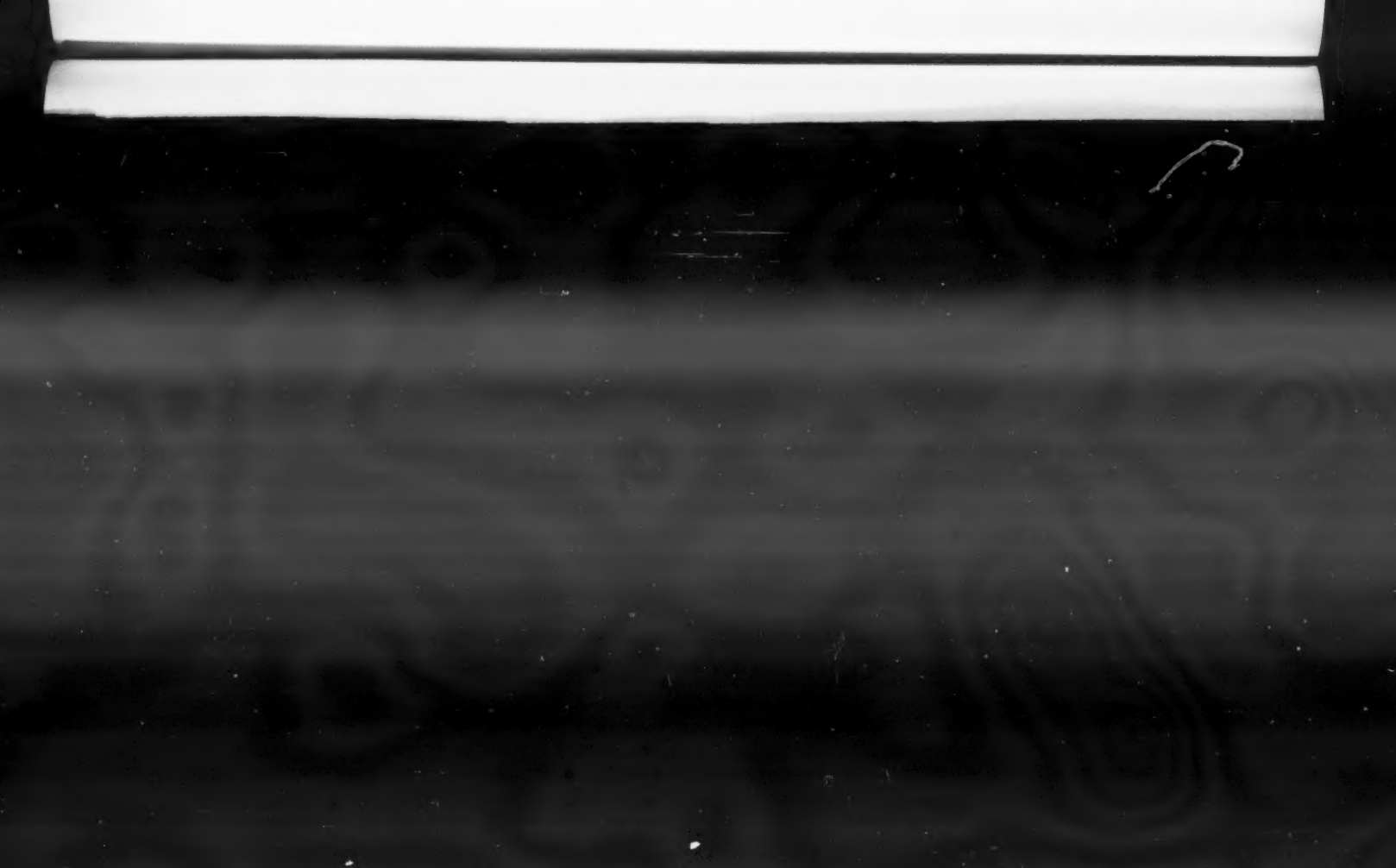
If we adopt Topping's statement that "strains of RMSF should be classified with reference to their virulence to guinea pigs" (1941) then we may conclude that our two strains originating from two partner patients and most probably from the same source of infection show significant differences in this respect. Our AD strain would correspond to Topping's "L" strain, known to be of lowest virulence for guinea pigs (fatality rate 4.4 per cent). We cannot ignore, however, the high virulence of both our strains in relation to man, for whom they were deadly in both cases. In other words, the virulence of RMSF for guinea pig does not necessarily reflect its virulence for man, and vice versa.

In comparing the symptomatology of our strains with that of the *Dermacentor andersoni* strain, only minor differences were noted in respect to incubation, type and length of fever. An important point of difference was, however, observed in regard to scrotal reaction. While orchitis accompanied by a dusky purple discoloration and necrosis of scrotal skin is a frequent symptom in the strain from Idaho scrotal lesions were originally only very occasionally observed in guinea pig transfer of our strains. In these few instances the reaction was either slight or of moderate degree only. It has to be noted, however, that the infrequency of the clinical evidence of scrotal reaction did not correspond to pathological findings, as we shall see later.

Contrary to frequent necrotic lesions of the skin on the soles and ears in guinea pigs of the strain from Idaho, such lesions were until recently only seldom noticed in our series. This applies, however, for one of our strains, namely, AD, but not for the SD strain. The latter showed after its fourteenth generation a marked increase in virulence, namely, a higher fatality rate and an almost constant scrotal reaction, to the similar extent as in the *Dermacentor andersoni* strain.

Other symptoms, such as superficial necrosis and scaling of the skin on the soles of guinea pigs of the SD series as well as necrotic lesions of the ears had also appeared recently.

As a whole, the gross pathology of guinea pigs infected with our strains of spotted fever is practically identical with the condition of the Idaho strain. A slight injection and swelling of the inguinal glands and to a lesser degree of the axilliary glands were noted almost on every post-mortem. A subcutaneous diffuse hemorrhage at the site of the virus injection was observed on several occasions. The parietal surface of peritoneum was frequently found injected and accompanied by injected viscera. The dominant changes were found in the spleen, which contrary to insignificant enlargement in experimental typhus (murine and louse-borne) was constantly found very enlarged (twice or three times the normal size). A dark purplish red color of the spleen was the rule, its consistency friable. Liver was normal or showed a yellow purplish discoloration.



Otherwise, no changes were noted by naked eye examination. The urinary bladder showed in several cases numerous minute hemorrhagic petechiae on the serous membrane and on the mucosa. The adrenals were invariably moderately or intensely injected, frequently hemorrhagic on the cut surface and swollen. Kidneys showed generally hyperemia and slight swelling. The tunica vaginalis was found congested in practically every case, also when clinically no scrotal reaction was ever noticed. It was found slightly edematous and adherent to the scrotum and some times to the injected testicles. No exudate was, however, present in the tunica. In other words, the condition can be determined as a subclinical reaction not prominent enough for a clinical diagnosis. The condition of the lungs can be classified as pneumonitis of various intensity. In a proportion of cases, a general congestion of moderate degree was noticeable, the lung surface being strawberry in color. In other cases, the color of the lungs was pearl greyish or uniformly pink. On this background, various in appearance, minute hemorrhagic petechial foci could be noticed, scattered over the lung surface and also present on the cut tissue. Sometimes the lungs were teeming with the above foci. Only in very few guinea pigs a definite consolidation of a portion of one or both lungs was observed.

The histopathological changes were most prominent in the tunica vaginalis where far reaching vascular lesions, perivascular infiltration, proliferation of the endothelium, thrombosis of the vessels and hemorrhages were characteristic (Photo 4). The same type of lesions of various gradation was found in other organs.

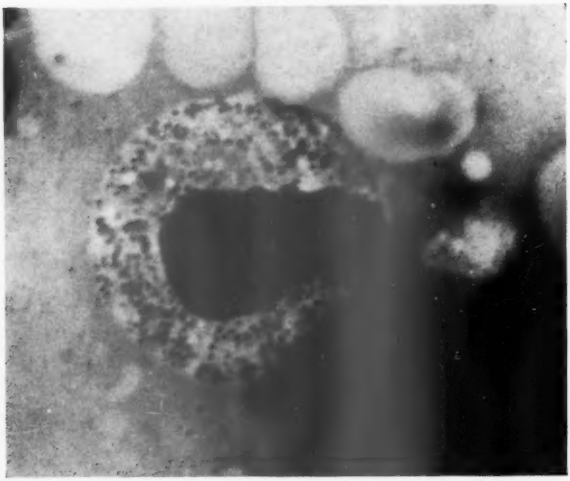
Microscopic and bacteriological examination of the organs did not reveal any evidence of bacterial infection.

DEMONSTRATION OF RICKETTSIAE

The first evidences of rickettsiae in the present cases were found in smears made from the liver of the girl about three hours after death. The smears were fixed in methyl-alcohol and stained with Giemsa. The rickettsiae appeared in the cytoplasm of large mononuclear cells as purple reddish stained coccoid bodies scattered in the cytoplasm either single or as diplococci. In places they were

clustered together. Among them short cocco-bacillary forms were also observed. (Photo 5.)

4. Tunica vaginalis of a spotted fever passage guinea pig showing profuse round cell infiltration and necrosis. Giemsa stain. 400 x.



5. Smear of the girl's liver (spotted fever victim) showing large mononuclear cell filled with intracytoplasmatic rickettsiae. Giemsa stain. 4000 x.

The search for rickettsiae was then continued in sections of various human organs fixed in Regaud's solution

and then stained with Giemsa for 24 hours and afterwards differentiated after Wolbach's method. Numerous mononuclear cells chiefly within perivascular inflammatory foci of the skin were found densely packed with minute coccoid bodies stained purplish red. The cytoplasm of these cells sometimes showed a distinct vacuolization. The cells containing these bodies were found in various situation: extravascularly but closely associated with the vessels, or engulfing a capillary, while in other instances a swollen endothelial cell or a smooth muscle cell of the vessel's wall contained the same type of inclusions. Agglomerations of these bodies were also seen free in subcutaneous tissue in clusters and resembling "microcolonies." Mononuclear cells containing rickettsiae were also found in myocardium, kidney, and were particularly abundant in hemorrhagic foci of the stomach wall of the boy.

In comparing our findings with those of Pincoffs and Shaw (1933) and with the description of Florman and Hafkenschiel (1940) referring to rickettsiae of the eastern type of spotted fever we found a striking similarity.

The rickettsial nature of the above described microorganisms found in our cases was supported by Dr. R. R. Parker, Director, Rocky Mountain Laboratory, who was kind enough to examine our material. According to his opinion "the pictures are very suggestive for rickettsiae."

Rickettsiae were then searched for in various organs of our passage guinea pigs but with negative results until the time when the virulence of the strains has increased and the scrotal reactions became prominent. They were then seen in smears and still more readily in sections of the tunica vaginalis. In smears from tunica scrapings two types were observed, namely, coccoid and bacillary. The first type appeared mostly as minute diplococci, lanceolate in shape sometimes giving the impression of a minute bipolar cocco-bacillus. They usually appeared in clusters. The slender bacillary forms were grouped together in bundles in which they were arranged parallel to each other. (Photo 6.) A pale bluish outer part can be distinguished from the purplish red inner structure in smears stained by Giemsa method. This description refers to extracellular organisms originating probably from disrupted cells, containing intracytoplasmatic organisms.

In sections of guinea pigs testis showing swelling and hemorrhage rickettsiae were seen in the tunica vaginalis. They appeared in swollen endothelial cells in areas of prominent vascular lesions and also in smooth muscle fibers of the arteriolae. These organisms are bacillary or coccobacillary in type, single or in bundles, their long axis ar-

6. Smear of Tunica vaginalis scrapings from a spotted fever passage guinea pig showing rickettsiae of coccoid and bacillary type. Giemsa stain. 1200 x.

ranged in parallel or vertical rows to the vessel's wall. In morphology and arrangement the described rickettsiae do not differ from the type known in Rocky Mountain spotted fever, except for the fact that in our strains the coccoid form was more frequently observed particularly in human tissues. On the other hand, the appearance of these two types of rickettsiae lies within the range of their pleomorphism, consequently, too much emphasis should not be placed on the particular form. Should, however, a given type be found constantly predominant in a local strain then it may be regarded as one of the characteristic feaures. In

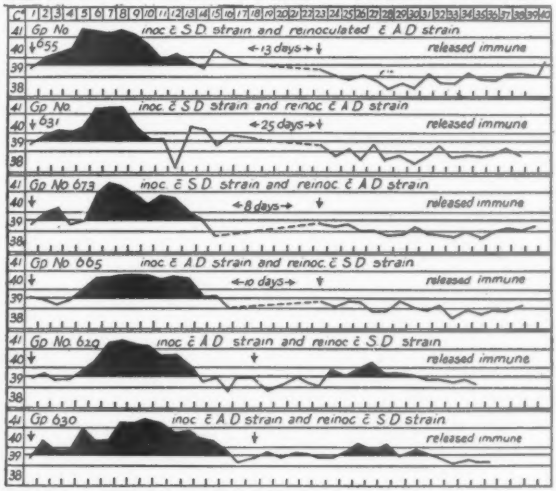
this regard it is of interest to note that the coccoid form of rickettsiae found in the "Tobia" spotted fever of Colombia has been emphasized by Patino Camargo (1941).

IMMUNITY TESTS.

The two isolated strains were first tested against each other, the less virulent one (AD) against the more virulent SD and vice versa.

TABLE 1

CROSS-IMMUNITY TESTS BETWEEN TWO SPOTTED FEVER STRAINS OF TEXAS ORIGIN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41
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Gp No 655
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released immune
Gp No 631
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←25 days→
released immune
Gp No 673
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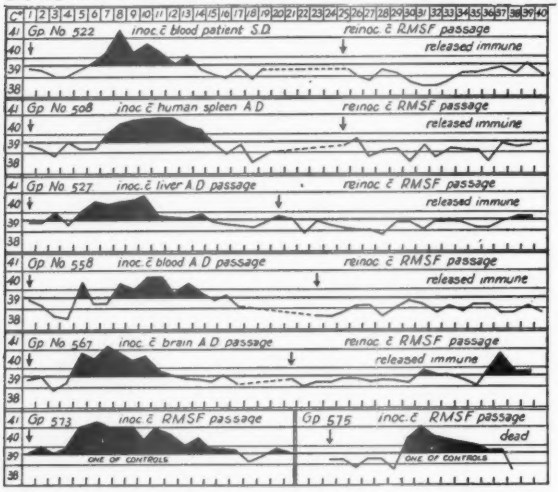
released immune
Gp No 665
inoc č A.D strain and reinoc. č S.D strain
←10 days→
released immune
Gp No 629
inoc č A.D strain and reinoc č S.D strain
released immune
Gp 630
inoc č A.D strain and reinoc č S.D strain
released immune

A series of five guinea pigs three of them having previously developed atypical fever and two which had a rather atypical course of the disease (protracted fever reaction or long incubation period) were tested after their recovery against SD strain. Out of the three typical convalescent guinea pigs one was reinoculated after ten days interval and remained afebrile during sixteen days' observation. The other two reinoculated after two and five days respectively after their fever fell to normal responded after six days with a mild febrile reaction—negligible as compared with the controls. This reaction was most probably due to the very short interval between their recovery and reinfection. Another group of five guinea pigs convalescent from the AD infection was tested for immunity against the same strain and the results were similar to the above series, namely

the typical disease in three guinea pigs afforded complete immunity while two animals which had an atypical course (low fever after twelve days incubation in one and negligible fever reaction in the other) developed atypical disease after reinfection. The next series consisted of six guinea pigs, all of of them convalescent after typical infections with SD strain. They were reinoculated after intervals from eight to twenty-five days with the AD strain.

TABLE 2

SPOTTED FEVER OF TEXAS ORIGIN TESTED AGAINST ROCKY MOUNTAIN SPOTTED FEVER



Four of them showed complete immunity while in one the immunity was partial of high grade as shown by a mild febrile reaction. Finally the SD strain was tested against the homologous SD infection in a group of four guinea pigs, all of them remaining afebrile after reinoculation, thus showing complete immunity. (Table I.)

Summarizing the above results we may conclude that the two strains isolated from two different patients of spotted fever have to be regarded as immunologically identical.

The next problem was to investigate the immunological relationship between our strains and the *Dermacentor andersoni* strain from Idaho. Eight guinea pigs convalescent from AD spotted fever were reinoculated after inter-

vals from six to ten days with the Idaho virus and proved to be fully immune to the reinfection. Same results were obtained with SD strain tested against the Idaho virus. (Table 2.)

Doubtful results in which only partial immunity or none were obtained originally in guinea pigs which recovered from Idaho spotted fever and were then tested against our strains. However, the repetition of these experiments on seven guinea pigs convalescent from *Dermacentor andersoni* infections and subsequently reinoculated at intervals from ten to forty-two days with SD or AD strains resulted in complete absence of any febrile reaction during eighteen days observation. (Table 3.) An immunological reciprocity has been thus established between Texas and Rocky Mountain spotted fevers. In addition to the above experiments tests were also carried out with louse-borne typhus virus of Spanish origin and with murine typhus of Texas. Six guinea pigs which had recovered from infection with Spanish typhus were subsequently reinfected after intervals from twenty to sixty days with spotted fever of Texas. Those reinoculated with AD ran a typical course of disease and recovered while the series reinfected with SD developed in all three cases prominent scrotal reactions and necrotic lesions on the soles. All three animals died.

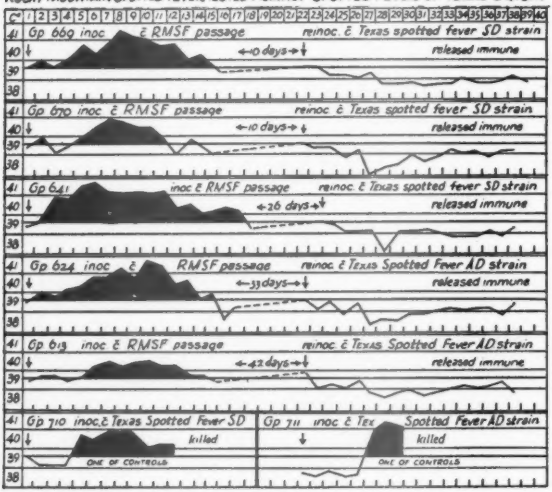
The above results show that not only there was no protection afforded by typhus exanthematicus infection but even a higher susceptibility to spotted fever developed. These findings do not correspond to those of Castaneda (1941) who came to the conclusion that "there is a definite immunological overlapping between spotted fever and typhus infection." Similar results were obtained when guinea pigs convalescent from three different typhus strains of murine type isolated by us from wild rats and human cases in Texas were reinoculated with spotted fever. Out of nine animals in one case only a complete absence of febrile reaction was noted, otherwise the remaining guinea pigs all developed typical spotted fever.

On the basis of the above results it was of interest in knowing whether the *Dermacentor andersoni* vaccine will protect against spotted fever of Texas. Two types of spotted

fever vaccine were used for this purpose: the tick-vaccine kindly supplied by Dr. R. R. Parker and Cox's egg-yolk-sac vaccine manufactured and generously furnished by Lederle Laboratories, New York. The first group of guinea

TABLE 3

ROCKY MOUNTAIN SPOTTED FEVER TESTED AGAINST SPOTTED FEVER OF TEXAS ORIGIN


C° 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40
Gp 669 inoc. ♂ RMSF passage
reinoc. ♂ Texas spotted fever SD strain
←0 days→
released immune
Gp 670 inoc. ♂ RMSF passage
reinoc. ♂ Texas spotted fever SD strain
←10 days→
released immune
Gp 641 inoc ♂ RMSF passage
reinoc. ♂ Texas spotted fever SD strain
←26 days→
released immune
Gp 624 inoc. ♂ RMSF passage
reinoc. ♂ Texas Spotted Fever AD strain
←33 days→
released immune
Gp 613 inoc. ♂ RMSF passage
reinoc. ♂ Texas Spotted Fever AD strain
←42 days→
released immune
Gp 710 inoc. ♂ Texas Spotted Fever SD
killed
ONE OF CONTROLS
Gp 711 inoc. ♂ Tex Spotted Fever AD strain
killed
ONE OF CONTROLS

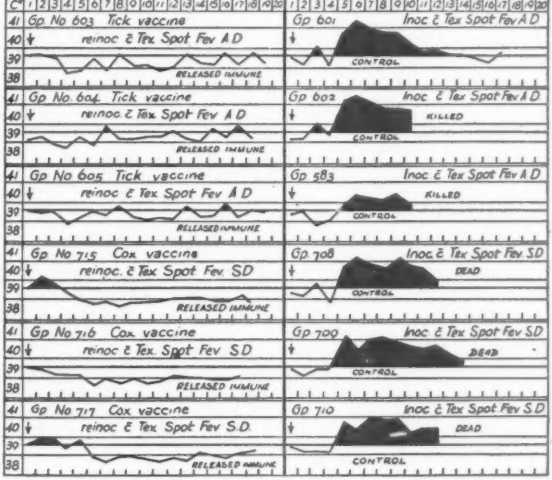
pigs was inoculated three times with 0.5 cc. of tick vaccine at weekly intervals and eight days later with the virus of spotted fever of Texas. No febrile reaction was noticed in any of these animals over seventeen days' observation, and they were released as immune while all the control animals reacted promptly and typically. Similar experiments were performed with the Cox's vaccine which proved to be just as efficient. (Table 4.)

It can be seen from the above observations that a complete immunological reciprocity has been established between the spotted fever of the Rocky Mountains and that of Texas. Each of these diseases occurs under very different physiographic and epidemiological conditions, the former being a *Dermacentor andersoni* infection while the spotted fever reported herewith was of *Amblyomma americanum* origin. In this respect it is of interest to note that

the spotted fevers of Brazil and Colombia in which the genus *Amblyomma* is one of the vectors also show an immunological identity with the Rocky Mountain type. (Dyer, 1933, Parker and Davis, 1933, Patino-Camargo, 1941.) In other

TABLE 4.

IMMUNITY OF GUINEA PIGS VACCINATED & ROCKY MOUNTAIN SPOTTED FEVER-VACCINE (TICK AND COX VACCINES) AGAINST SPOTTED FEVER OF TEXAS ORIGIN



words, on the basis of our present knowledge the diseases belonging to the spotted fever group of this hemisphere are immunologically identical irrespective of their epidemiology and local geography.

SUMMARY AND CONCLUSIONS.

Four cases of spotted fever occurred in June 1942 in the central section of the Gulf Coast of Texas, where the natural conditions are particularly favorable for a heavy tick infestation.

The disease was fatal for two children who were newcomers to the locality, arriving there at the height of the tick season. On the basis of the past records and observations previously made by Dr. Boyd Reading this section seems to be endemic for spotted fever.

An extensive tick survey carried out on that area revealed *Amblyomma americanum* in great abundance which

was the only tick species present. This fact in addition to the tick bite history of the cases and the recovery of *A. americanum* from the family of the victims are of strong evidence that in this spotted fever outbreak *A. americanum* was the carrier. Consequently, the disease can be attributed to a new vector in addition to the ticks known as vectors of spotted fever in the United States. A strain of spotted fever virus was isolated from each of the two fatal cases and these two strains are maintained in guinea pigs by transfers. The two strains differ from each other as to their virulence and pathogenicity for guinea pigs but proved to be immunologically identical.

The experimental disease in guinea pigs corresponds clinically as well as immunologically to the *Dermacentor andersoni* strain.

Rickettsiae were demonstrated in sections of human tissues of the two fatal cases and in organs of transfer guinea pigs. The rickettsiae appear in two morphological types: as coccoid and bacillary organisms, the former corresponding to the characteristics of spotted fever reported from Colombia (South America).

Inoculation of emulsion of several *Amblyomma americanum* ticks from dogs and cattle found on the ground of the spotted fever outbreak into guinea pigs produced in some of them a febrile disease followed by partial immunity to subsequent infection with spotted fever.

The new epidemiological aspect of spotted fever reported herewith as well as similar observations from South America where the genus Amblyomma is also a carrier suggest that the geographical designation of spotted fever should be replaced by epidemiological criteria. In this respect two principal members of the spotted fever group of this hemisphere can be distinguished, one transmitted by the genus *Dermacentor*, the other by the genus *Amblyomma*. The latter type includes a great portion of Texas and a large part of South America as a related epidemiological zone.

The observations on the local epidemiology of the disease deserve also attention from a war-time angle. The locality where the outbreak took place is a typical war-time boom town, where owing to acute shortage in housing ac-

commodation workers are compelled to live in wooded areas, thus being exposed to tick bites and to the danger of infection. It is obvious that the expansion of the war industry in the Gulf Coast of Texas may create in future tick seasons similar environmental factors.

ACKNOWLEDGEMENTS

The writers are grateful to the Department of Pediatrics, especially to Drs. Boyd Reading, Chairman of the Department, and Hugo Klint for giving them full access to their clinical material.

The authors are also indebted to the Department of Pathology, particularly to Drs. Paul Brindley, Chairman of the Department, and Henry Sweets. Great credit is due Miss Berly Brewer, chief technologist for her continued valuable help and interest in this problem.

The cooperation of the Department of Veterinary Parasitology of the Agricultural and Mechanical College of Texas, particularly that of Dr. H. L. van Volkenberg proved again of great value for these studies.

The writers wish to express their deep appreciation to Dr. Chauncey D. Leake, Dean, and Dr. Carl A. Nau, Chairman, Department of Preventive Medicine and Public Health, for their interest and stimulating encouragement toward the continuation of this work.

The present investigations were greatly benefited by the interest and authoritative advice of Dr. R. R. Parker, Director, Rocky Mountain Laboratory, U. S. Public Health Service, Hamilton, Montana.

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NOTE

While this paper was in press a note appeared in the Public Health Reports (March 19, 1943)* announcing that the tick **Amblyomma americanum** had been found by R. R. Parker, G. M. Kohls and E. A. Steinhaus infected with Rocky Mountain spotted fever in Oklahoma. The findings of these authors, gave therefore, a final proof of our previously reported observations incriminating this tick as a new vector of spotted fever (Anigstein and Bader, 1942).

*Amblyomma americanum a vector of Rocky Mountain spotted fever, Public Health Reports, 1943, 58, 491.

PEROXIDES FOR WOUND HEALING

A recent note *(J. Amer. Med. Asso.,* 119: 101, May 2, 1943) proposed certain advantages of benzoyl peroxide over zinc peroxide or sulfonamides in treating wounds or burns. Benzoyl peroxide was suggested by A. S. Loevenhart *(Therap. Monatsh.,* 12: 426, 1905) as an effective nonirritating oxidizing antiseptic with local anesthetic properties. R. A. Lyon and T. E. Reynolds *(Proc. Soc. Exper. Biol. Med.,* 27: 122, 1929) found that it promotes wound healing. That zinc peroxide may prevent gas gangrene in wounds was demonstrated by F. L. Meleney *(Ann. Surg.,* 101: 997, 1935). A combination of zinc peroxide and sulfathiazole was recommended for this purpose by G. B. Reed and J. H. Orr *(War Med.,* 2: 79, 1942).

There is evidence that sulfonamides inhibit wound healing and irritate tissue (F. W. Taylor, *J. Amer. Med. Asso.,* 118: 959, Mch. 21, 1942). This is to be expected if the mechanism of action of sulfonamides is to inhibit growth, either by interfering with such growth promoting substances as p-amino benzoic acid (D. D. Woods, *Brit. J. Exper. Path.,* 21: 74, 1940), or by blocking enzyme systems necessary for growth (F. H. Johnson, *Science,* 95: 104, Jan. 23, 1942). Of course, anything that reduces infection in a wound will ultimtaely aid wound healing. But the sulfonamides in a sterile wound may reduce the rate of healing.

Benzoyl peroxide has advantages over sulfonamides for direct dusting into wounds to inhibit gas forming organisms in that it promotes wound healing in addition to exerting an effective antiseptic action without local irritation or injury. It is better than zinc peroxide in that it is locally anesthetic and does not leave an insoluble residue which may provoke a foreign body reaction.

A considerable number of peroxides are available. The most promising seems to be urea peroxide, formed by combining one molecule of urea with one of hydrogen peroxide. It is a white stable crystalline solid, decomposing at 60° C. It has a brief cool taste and its 10% water solution is slightly acid. With an oxidizing antiseptic action greater than hydrogen peroxide and probably as prolonged as that of benzoyl peroxide, urea peroxide may also show slight

local anesthetic effect. On hydrolysis of urea peroxide, urea remains which may aid wound healing by autolysis of necrotic tissue. It has already been shown (C. V. Fisher, N. J. Accousti and M. R. Thompson, *J. Amer. Med. Asso.*, 122: 855, July 24, 1943) that urea peroxide is the most effective agent for preventing bacterial contamination in sulfonamide ointments. It has also been found to be useful in promoting wound healing and in treating chemical burns (D. F. Marsh and G. A. Emerson, personal note). Urea peroxide thus clearly deserves careful clinical trial to estimate its general usefulness in handling wounds and burns.

C. D. L.

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THE EFFECT OF EXCESS PANTOTHENIC ACID, PARA-AMINO BENZOIC ACID AND INOSITOL ON ADAPTATION OF RATS TO LOWERED ATMOSPHERIC PRESSURES

C. U. DERNEHL, J. K. CLINE, H. G. SWANN AND W. D. COLLINGS*

Many investigators have considered recently the possibility of adrenal dysfunction as playing an important role in chronic altitude sickness and pilot fatigue. Armstrong pointed out the similarity of chronic altitude sickness to early Addisons disease and observed adrenal hypertrophy in rabbits exposed to lowered atmospheric pressure. Girragossintz and Sundstroem noted a similar reaction in rats and also showed an increased demand for adrenal cortical hormone in rats exposed to lowered atmospheric pressures. Dohan has likewise shown that rat adrenals hypertrophy when subjected to anoxia. Langley and Clark confirmed the work of Girragossintz and Sundstroem and further demonstrated that the increased demand for cortin was limited to the first three days of exposure. In the recent excellent monograph of Sundstroem and Michael, investigation of the effects of cortin, flavin phosphate, and on other aspects of adrenal function during anoxia are extensively described.

Mills and his co-workers, as well as Salmon and Engel, found that animals placed on a diet deficient in pantothenic acid developed a hemorrhagic adrenal necrosis and a graying of the fur. Likewise Daft and his group noted a similar adrenal necrosis and observed in addition, adrenal atrophy and fat depletion of the adrenal cells. Not only did they show that pantothenic acid protects against the pathological change, but also that pantothenic acid, in doses of 100 gamma daily for ten days, was able to restore the adrenals to their normal condition as compared to control animals. Further work has shown that para-amino benzoic acid plays a part in the graying of rats. Martin (a) found that animals placed on a diet deficient in pantothenic acid suffer from a deficiency of inositol as well, and that while

* From the Laboratories of Physiology and Preventive Medicine, University of Texas Medical School. Submitted for publication February 10, 1943.

inositol prevents the hemorrhagic adrenal necrosis, it does not effect the graying of the fur.

A consideration of the above facts raised the question as to whether any of the above mentioned compounds might influence the rapidity or extent of adrenal hypertrophy in albino rats exposed to lowered barometric pressures. In the course of experiments to determine this, there was found to be a 26 per cent increase in adrenal weight of rats exposed to low barometric pressures as compared to non-exposed control rats. More startling, however, was the weight loss produced in these animals. More detailed studies by our group soon demonstrated that this weight loss was largely a manifestation of insensible water loss. Inasmuch as it was possible to demonstrate only a 5 per cent decrease in adrenal weight of pantothenic acid treated animals as compared to control animals, while the difference in weight curves of the two groups at times amounted to 10 per cent difference, it was apparent that the weight curves of the animals were a better measure of their general reaction to pantothenic acid, para-amino benzoic acid, and inositol administered during periods of exposure to lowered barometric pressures.

Due to present conditions it was impossible to obtain suitable pressure chambers. However, several satisfactory chambers were constructed in the following way. The bottom was cut out of a standard 30-pound ether drum and a moderate weight 14-inch steel frying pan was soldered to the open end of the drum. Previous to attaching the frying pan to the drum, a circular opening, slightly smaller than the inside diameter of the lid of a 12-inch vacuum desiccator, was cut in its center. Around this opening there was cemented a heavy rubber gasket which acted as a base for the desiccator lid used as a removable closure. The lid was clamped into place by two carpenters "C" clamps attached to the projecting sides of the frying pan. Room air was brought into the rear of the chambers and exhausted through the opening in the desiccator lid. A wire cloth floor, below which was placed sawdust, allowed for easy cleaning of the chamber. The series of chambers was connected to a large ballast tank (30-gallon hot watertank) which was evacuated by a laboratory vacuum pump, and the degree

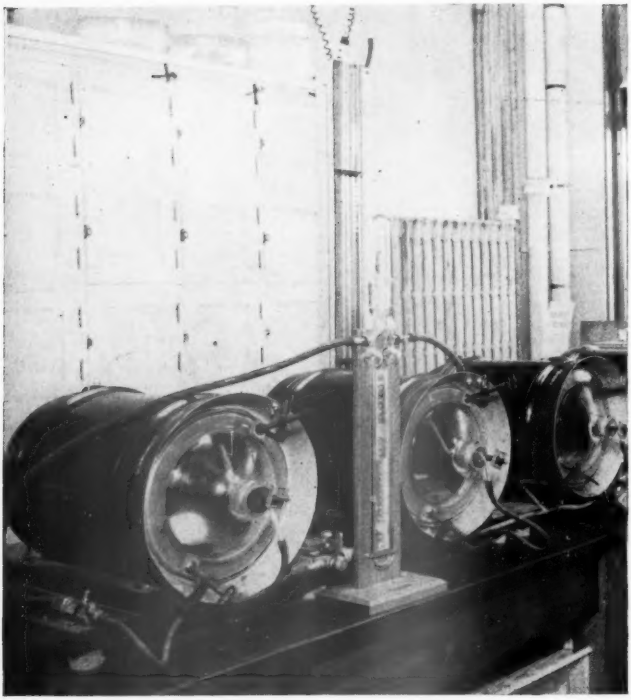
of reduced pressure was controlled by a manostat which kept the pressure constant within one or two millimeters of mercury. A flowmeter was placed at the intake end to control the volume of fresh air admitted. As a routine measure the air was allowed to enter at the rate of 2,000 cc. per minute since it was found by gas analysis that this rate kept the carbon dioxide level low and supplied ample amounts of oxygen. All experiments were run at a pressure of 380 millimeters of mercury.

The rats were fed a ration of Purina Dog Chow, and ample supplies of both food and water were available at all times. All experimental animals received the various compounds by mouth except for three small rats which received 100 gamma of pantothenic acid a day by subcutaneous injection. Test animals received the various compounds for six days before exposure to lowered barometric pressures and were given the same daily dosage during the stay in the chamber. They were continuously exposed to reduced pressure except for one-half hour a day during which time the chambers were cleaned, the animals weighed, and the compounds administered. Control animals were run under identical conditions, although not simultaneously. While many experiments were continued beyond the time limit shown in this paper, it was found that the first five days were the critical days and that all rats continued to gain weight after this period.

The following dosages were given to all animals regardless of weight or age:

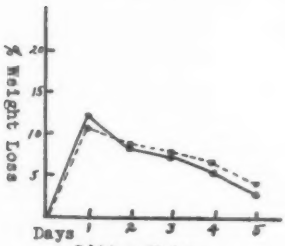
Pantothenic acid	100 gamma
Para-amino benzoic acid	1 mgm.
Inositol	10 mgm.

A study of data from experiments which will be reported at a later date showed that animals exposed to low atmospheric pressures at high temperatures lost more weight than did those exposed at more moderate temperatures. Since, however, the greater part of this work was done during a period in which the temperature seldom varied more than a few degrees day and night, it is felt that any variations due to differences in temperature may be considered negligible.



Low pressure chambers and regulating apparatus.

PANTOTHENIC ACID
SUB-CUTANEOUS INJECTION
(Fig. 4)



Litter Mates
Weight 87 gm.

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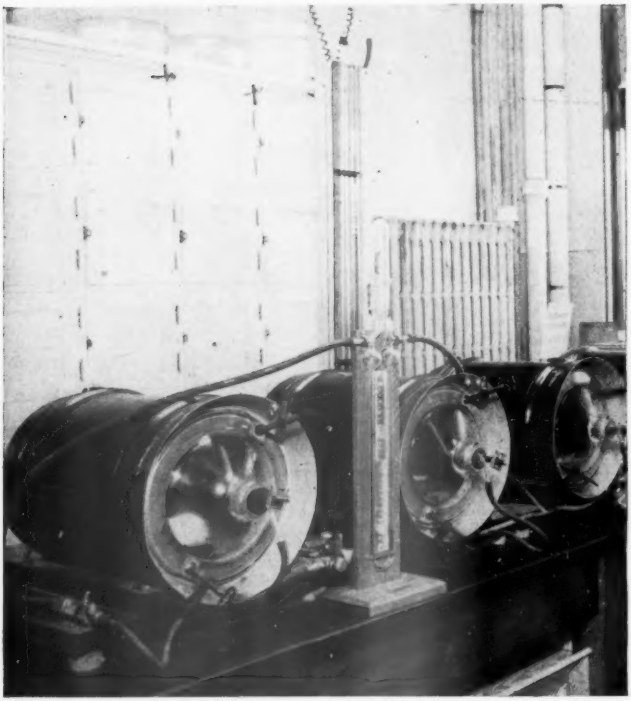
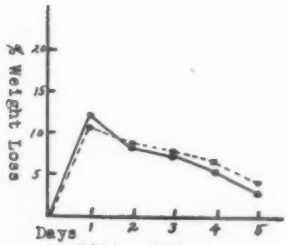
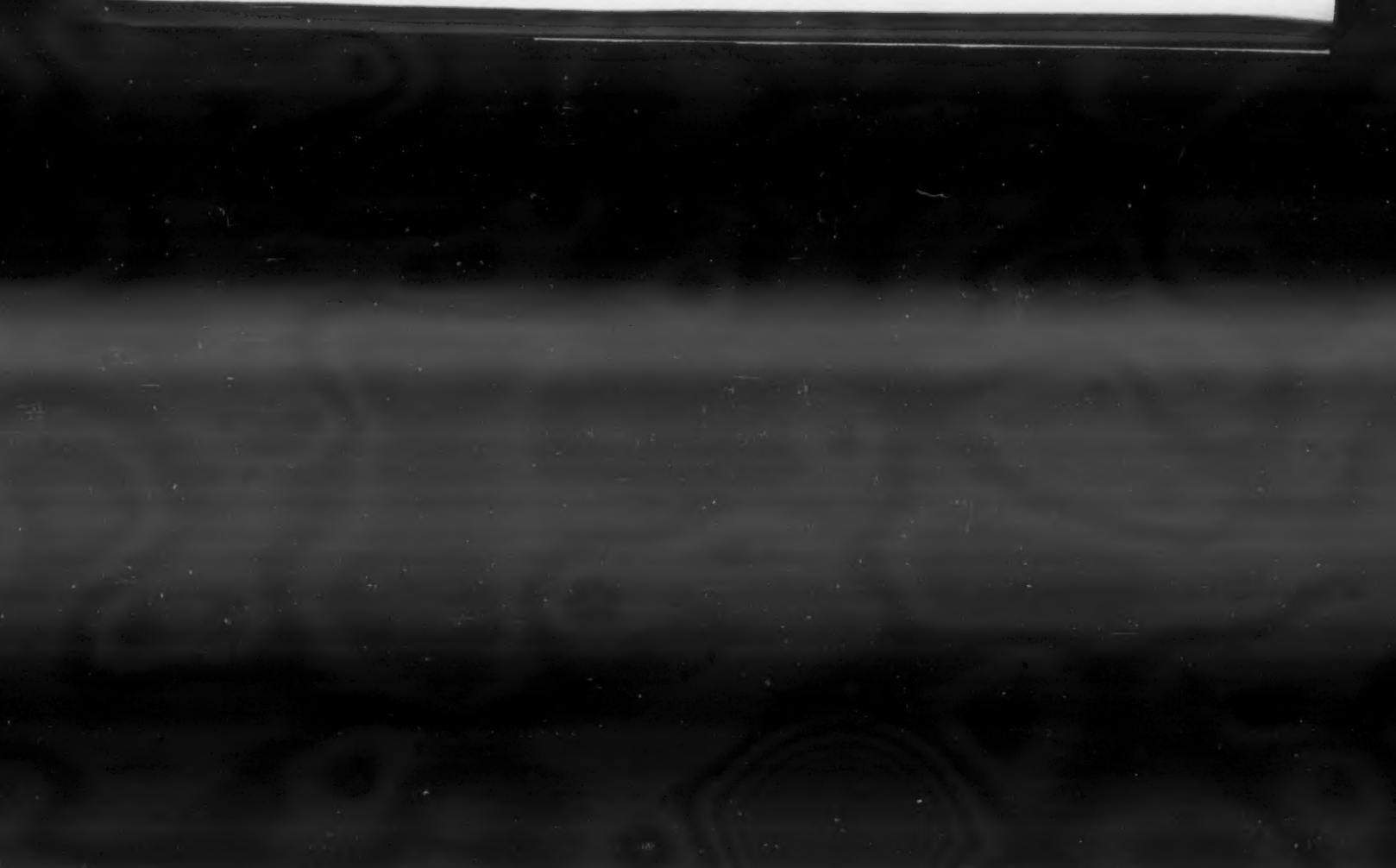


Low pressure chambers and regulating apparatus.

PANTOTHENIC ACID
SUB-CUTANEOUS INJECTION
(Fig. 4)



Litter Mates
Weight 87 gm.



RESULTS.

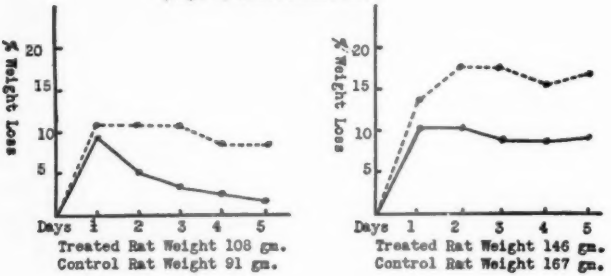
All weight losses recorded are computed as per cent weight loss as compared to the weight of the animal on the day it was placed in the chamber.

Pantothenic Acid (Fig. 1): The young rats showed an initial weight loss which closely approximated that lost by control rats, whereas the older group of treated rats lost 4 per cent more weight than did their control group. On succeeding days the young group retained their weight and on the fourth and fifth days showed a return toward normal, while the control group was rapidly regaining its initial weight after the 10 per cent weight loss on the first day. The older group of rats exhibited further weight loss on the second day at which time it approached 18 per cent. On the fourth day recovery had begun. The loss on the fifth day was not explained but was not considered important since succeeding days (not shown in curves) showed a tendency toward regaining the initial weight. In the small group receiving 100 gamma by injection there was no significant deviation from the controls. *(Fig. 4.)*

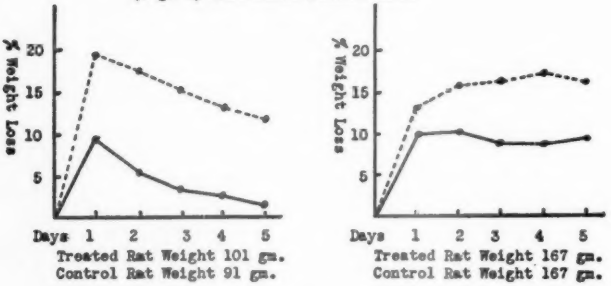
Para-Amino Benzoic Acid (Fig. 2): The young group of treated rats lost 19 per cent of their weight the first day as compared to 10 per cent for the control group. On succeeding days there was an immediate tendency to regain weight with the curves of the treated and control rats closely paralleling each other. The older group of rats lost 4 per per cent more weight the first day and continued to lose small amounts of weight on succeeding days showing no tendency to recover until the fifth day. Rats in the young group showed a striking red incrustation of the whiskers, eyes, and paws. The significance of this will be discussed later.

Inositol (Fig. 3): The initial weight loss of treated and control young rats differed by an amount that was within limits of variability. On succeeding days the treated rats continued to lose weight until a maximum loss of 20 per cent had been reached on the fourth day following which recovery began to take place. In the adult group the initial weight loss of treated and control animals was very similar, while on succeeding days the treated animals lost a little more weight. Recovery began on the fifth day.

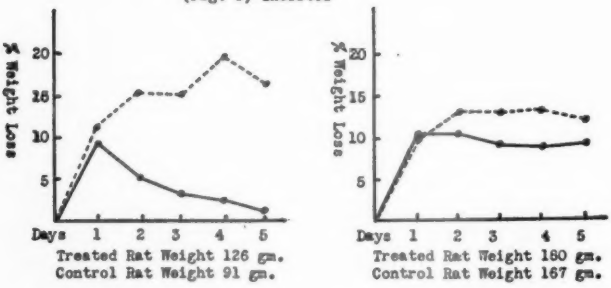
(Fig. 1) Pantothenic acid*



(Fig. 2) Para-amino Benzoic acid



(Fig. 3) Inositol



* Dotted lines represent treated animals. Solid lines represent control animals.

The difference in the control curves of the young and adult rats was attributed to the more rapid adaptation exhibited by young animals to changes in environment combined with the more rapid growth rate exhibited by animals of this age.

DISCUSSION.

There was no evidence in these experiments that increased weight loss was due to toxic action of the compounds used. Pantothenic acid on sub-cutaneous injection has been shown to have no deleterious action, and the compound has been given in doses of 200 gamma daily with no ill effect. Dosages for other compounds used were those commonly reported as necessary for maintenance of health in the rat. Absence of toxicity is further indicated by the fact that all animals had a normal growth curve in the six-day period before exposure.

The young rats receiving para-amino benzoic acid and having the red incrustation of the whiskers, eyes, and paws were of particular interest. The lesion has been attributed to deficiencies of riboflavin, and more recently of pantothenic acid. Smith and Sprunt produced similar lesions by water deprivation. This has been confirmed by Figge and Atkinson. Smith showed that such lesions produced by water starvation were not affected materially by administration of pantothenic acid, riboflavin or other members of the B group of vitamins. Brewers yeast had only a minimal effect on the lesions. From these results both groups concluded that pantothenic acid and riboflavin may play a part in water metabolism. Smith believes that this is true in spite of her lack of results following the administration of vitamins.

We can offer no explanation of the results obtained. The absence of the three compounds used is known to have certain limited effects on the living organism, but the site and extent of their action is as yet largely conjecture. There is the possibility that the compounds may have a diuretic effect, especially in the case of para-amino benzoic acid where it appeared that the yellow staining caused by excrement was increased over the amount usually seen in our rats. This remains to be checked by more detailed studies.

The fact that the greater part of the weight loss is due to loss of water, and the fact that the adrenal gland is intimately associated with water metabolism and response to anoxia, points to the possibility that the degree of weight loss may be a measure of adrenal adaptation during expos-

ure to low barometric pressure. Since Langley and Clark have shown that the added load on the adrenal lasts only the first three days and yet the animals continue to gain weight on following days, one would be justified in believing that some other means of adjustment exists and that the increased adrenal activity merely serves to tide the organism over the initial period until the secondary more permanent adjustment is fully active. Ingle has shown that under conditions demanding increased adrenal hormone output, the adrenal gland reaches its maximum hypertrophy the first 24 hours. Langley and Clark placed this time limit at 48 hours. Thus the fact that control animals in our studies either weighed the same or gained weight on the second day may indicate that a more permanent adjustment mechanism is already beginning to exert its effect in the second 24-hour period. That our results may indicate some interference with such a dual adjustment mechanism is not improbable as can be seen from the following paragraph.

An interpretation of the curves based on the above suggestion would have the following results. In the young rats pantothenic acid and inositol had no action on the adrenal since the first day's weight loss was similar to that of controls *(Figs. 1 and 3)*. But pantothenic acid had a slight and inositol a severe action on the secondary adjustment mechanism as shown by progressive weight loss on succeeding days. Para-amino benzoic acid, however, had a detrimental effect on the adrenal (as shown by the marked increase in weight loss on the first day) and the adjustment was left entirely to the secondary mechanism, which was not affected since the recovery curve closely parallels that of the control animals *(Fig 2)*. In the adult rats only inositol had no effect on the adrenal while pantothenic acid and para-amino benzoic acid had a slight adverse effect. All three compounds had an adverse effect on the secondary adjustment in varying degree. Further experimental work is necessary to clarify the nature of this secondary adjustment.

There is furthermore the question of a change in intestinal flora brought about by the change in the growth medium. Thus Martin (b) has shown that animals fed on a

diet lacking only para-amino benzoic acid and inositol developed normally. But if either of the above alone were added to the diet the animal developed signs of a deficiency which could be prevented by the addition of the other factor. The addition of both factors together permitted normal growth. From his studies Martin concludes that the addition of para-amino benzoic acid to the diet causes an inositol deficiency either by stimulation of organisms that use inositol for growth or by inhibition of organisms that form inositol. Likewise the addition of inositol to the diet may stimulate the growth of organisms which destroy pantothenic acid thus precipitating a deficiency in that substance.

The mode of action of these compounds remains obscure since the whole of the changes that take place in the body economy during the adjustment to low barometric pressures are not known. Whether the adaptation lies in the field of hormonal readjustment or in changes in the enzyme systems of the body, or both, cannot as yet be stated. Of interest in this connection is the recent work of Lawson showing that sulfanilamide apparently increases altitude tolerance. It is also known that sulfanilamide is antagonistic to carbonic anhydrase, and that para-amino benzoic acid is mutually antagonistic with sulfanilamide. Thus it is possible that when administered to animals exposed to low barometric pressures, sulfanilamide exerts its beneficial effect by means of its mutual antagonistic action with para-amino benzoic acid. Further studies under more carefully controlled conditions are now in progress.

CONCLUSIONS.

I. Pantothenic acid, para-amino benzoic acid, and inositol, when fed in excess of the amount found in a balanced diet of white rats exposed to reduced pressure, produced an increased weight loss as compared to control rats. The mechanism involved in this increased weight loss is not known.

II. In addition to the initial adrenal response a secondary adjustment mechanism to the effects of altitude is postulated.

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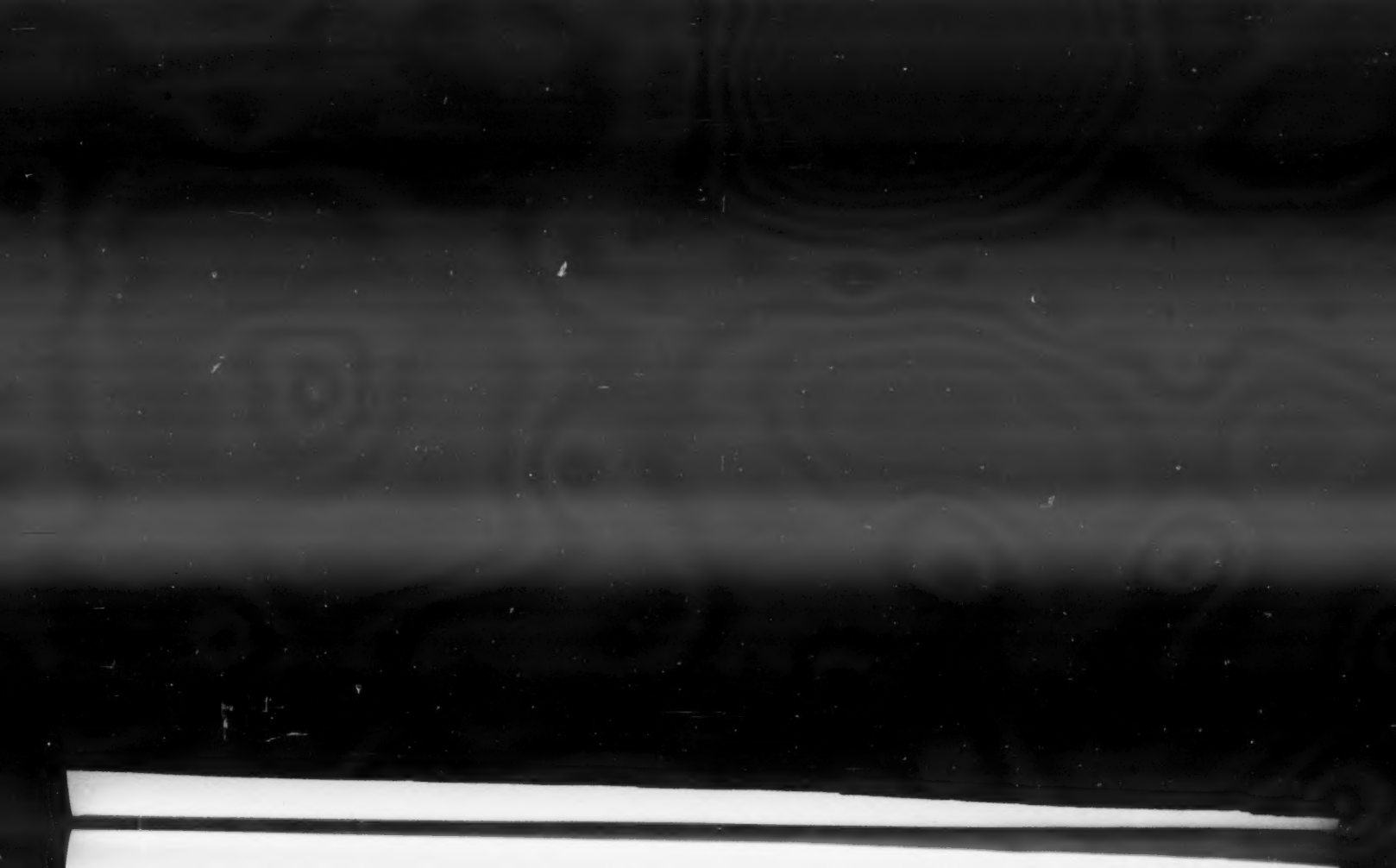

THE PERICARDIAL SAC USED AS A CARDIOMETER*

RAYMOND GREGORY AND PAUL L. EWING

Graphic recording of changes in cardiac volume is frequently used in teaching pharmacology and physiology as well as in investigations in these fields. Different types of cardiometers have been devised which are satisfactory under ideal conditions. Difficulties are frequently encountered, however, by medical students and others without special technical training. These difficulties interfere with accurate recording of the physiological response. In the first place, it is usually necessary to have a variety of sizes of cardiometers to fit the hearts of various sizes of animals. There is often difficulty in putting the cardiometer in position in the chest and on the heart. Finally, if the rubber membrane fits the base of the heart sufficiently tightly to prevent leakage, there may be interference with normal filling and emptying of the heart.

To obviate the difficulties referred to, we have devised a technique which employs the pericardial sac as a cardiometer. While this has been done primarily for student use, we believe its several advantages may lead to general use. Each heart is already enclosed in its own potential oncometer, making unnecessary special equipment; there is no chance for leakage in the oncometer, provided the recommended cannula is tied in securely; interference with normal function of the heart is minimized; insertion and fixation of the cannula is much simpler than a proper application of the ordinary cardiometer; and finally, changes in volume of the entire heart may be recorded by this method. It has been shown (Barnard) that the dog's pericardium is practically inextensible and that it exerts (Wilson and Meek) a marked restraint to diastolic dilatation of the heart at venous pressures as low as 0 to 2 cm. of water.

A special cannula suitable for tying into the pericardial sac has been designed. It is shown in Figure 1 and has the following features: A 17 cm. length of eight millimeter glass tubing is flanged on one end and has a bulb of approximately ten cubic centimeter capacity blown about three

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centimeters above the flanged end. Three centimeters from the opposite end, a side arm of four millimeter glass tubing is attached. This serves to connect the cannula to a recording tambour.

After the chest has been opened and artificial respiration established, the pericardium is grasped near the apex with two hemostats about one centimeter apart. A small slit sufficient to admit the flanged end of the cannula is then made in the parietal pericardium between these two forceps and the pericardium is tied securely around the cannula. Care is necessary to insure no leakage at this

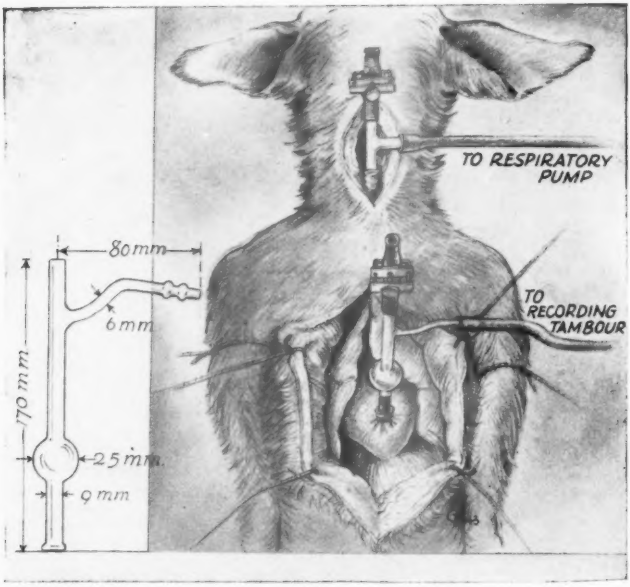

Figure 1.

point. For this reason, it is advisable to avoid a purse-string suture placed in the pericardium by needle. The cannula is then clamped vertically and connected to the recording tambour. It is esential that the cannula be inserted as close to the apex as possible. When it is placed too far toward the base, friction of the heart against the cannula may cause rupture of a coronary artery. A sufficient amount of warm light liquid petrolatum to bring

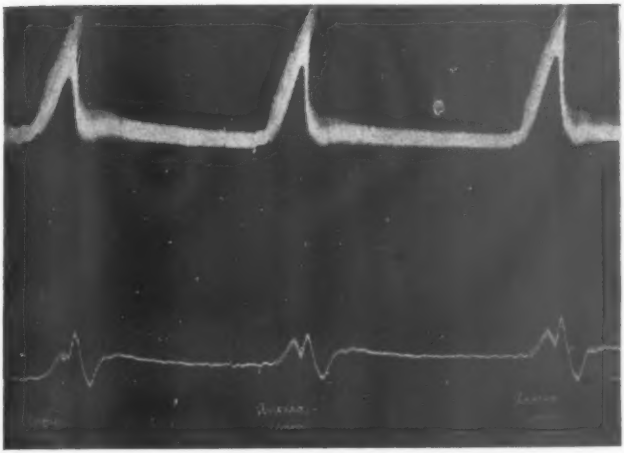

Figure 2. Showing a series of changes in the cardiac volume produced by cardiac volume produced by anoxia of one minute's duration. Top curve is the cardiac volume as recorded by the pericardial sac used as a cardiometer connected to a recording tambour of the Ash type. Middle curve is a recording of the blood pressure tracing obtained by connecting the carotid to a mercury manometer. The base line represents time and zero blood pressure. Upstroke shows an increase in volume of the heart. Downstroke shows a decrease in volume of the heart.

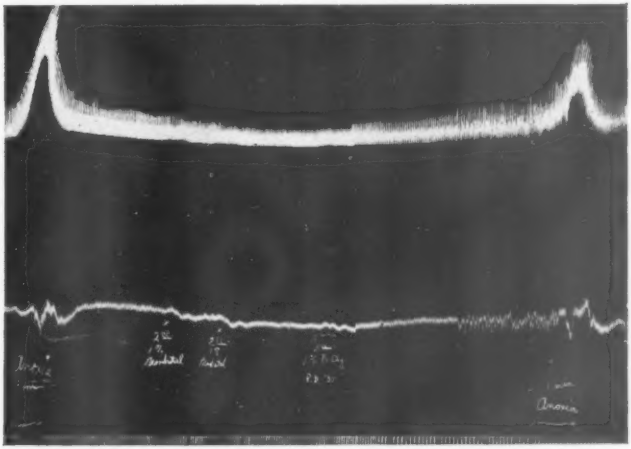

Figure 3. Showing the difference in response of the heart to anoxia of one minute's duration during and after the administration of a total of 32 cc. of a 1.5 dilution of standard tincture of digitalis. Top curve is the cardiac volume as recorded by the pericardial sac used as a cardiometer connected to a recording tambour of the Ash type. Middle curve is a recording of the blood pressure tracing obtained by connecting the carotid to a mercury manometer. The base line represents time and zero blood pressure. Upstroke shows an increase in volume of the heart. Downstroke shows a decrease in volume of the heart.

the level of the oil to the bottom of the bulb of the cannula is introduced through the open end of the cannula which is then closed by a clamped rubber tube. The angle at which the side arm comes off the shaft of the cannula prevents oil from running into the rubber tube leading to the recording tambour.

Figures 2 and 3 are kymographic records made with the method described.

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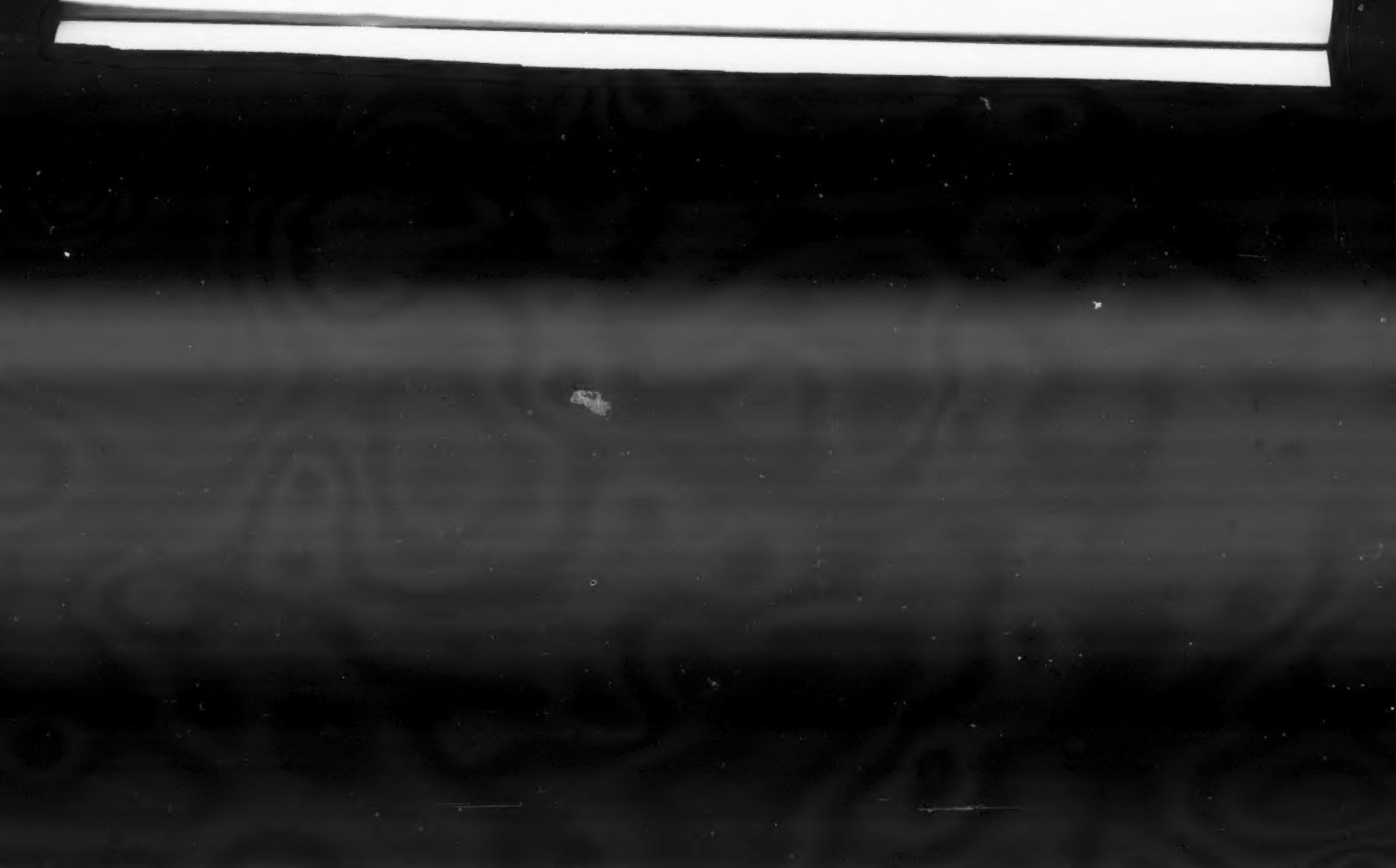

STUDIES IN ELECTROPHORESIS OF CELLS AND MICROORGANISMS

A NEW MACRO-ELECTROPHORESIS APPARATUS AND METHOD FOR REGIONAL ISOLATION OF PROTOZOA FROM BACTERIA AND FOR STUDIES OF ELECTRICAL CHARGE AND VELOCITIES OF FILTRABLE VIRUSES*

BY A. PACKCHANIAN*

The object of this communication is to describe four new types of macro-electrophoresis apparatus. Each type consists of a series of cells which can be utilized in experiments under strictly sterile conditions. These types of apparatus make possible the isolation of certain protozoa from a mixture of protozoa and bacteria and are also suitable for studying the electrical charge and velocity of filtrable viruses; they can also be used in studies of transference number of ions.

DESCRIPTION OF APPARATUS.

Macro-electrophoresis Apparatus Type A: The set-up which is illustrated in Figure 1 consists of 7 cross-shaped cells (the number can be increased when necessary), 4 two-way stopcocks, 2 three-way stopcocks, 2 "U" tubes, and 2 non-polarizable electrodes. These parts are connected with each other by thick-walled pure amber rubber tubing and are assembled on a suitable board stand. The direct current used in the experiment is regulated by resistance boxes, and the readings are made with a milliameter (ranging from 15 to 150 m. a.), and a voltmeter (ranging from 250 to 2500 volts).

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* A part of this work was done in the Department of Bacteriology and the Department of Colloid Chemistry, University of Michigan, Ann Arbor, Michigan, during 1929-1933.

The writer wishes to express his sincere thanks and gratitude to Dr. F. G. Novy, Professor of Bacteriology, and to Dr. F. Bartell, Professor of Colloid Chemistry, University of Michigan, for their kind interest in this work. Appreciation is also due to Dr. W. A. Bychinsky for his assistance in electrical measurements.

The cross-shaped glass cells (Figs. 1 and 2) have two vertical and two horizontal arms. Between adjacent cells are inserted two-way stopcocks which are connected to the horizontal arms of the cells by rubber tubing. The ends

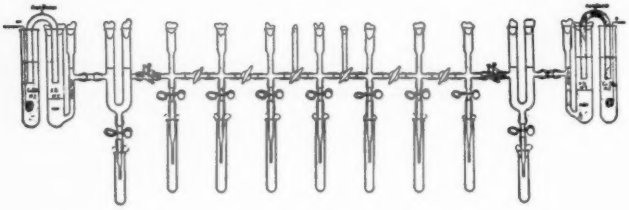


Fig. 1 – Micro-Electrophoresis Apparatus – Type A

of the horizontal arms of the cells and the stopcocks touch each other and are held together by means of rubber tubing. On either side of the sample-receiving cell there is located, in place of the two-way stopcock, a three-way stop-

A

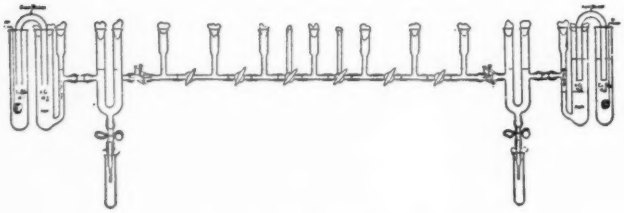


Fig. 2 – Micro-Electrophoresis Apparatus – Type B

cock with its third arm in an upright position. To the lower arm of each cell a small glass pipette is attached by means of soft amber rubber tubing, carrying a pinch-cock clamp. The upper arm of each cell is marked horizontally by an etched line near the base.

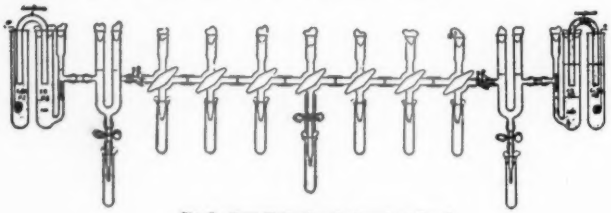
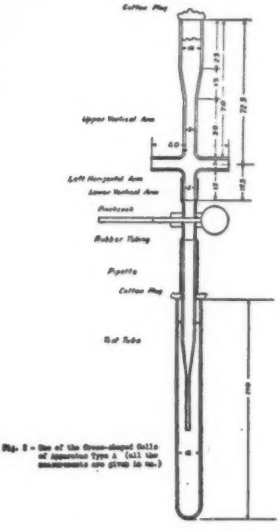
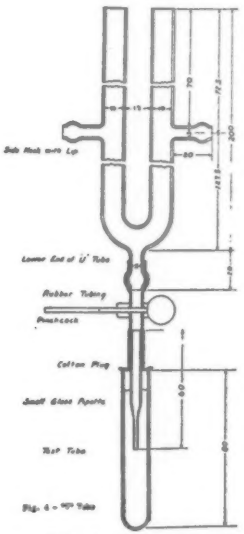
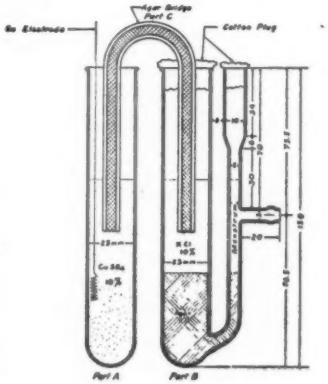


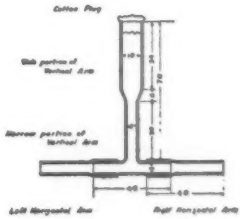
Fig. 3 – Micro-Electrophoresis Apparatus – Type C





The non-polarizable electrodes are illustrated in Fig. 1 and 3. Each unit consists of three parts. Part A is a simple test tube containing 10 per cent $CuSO_4$ solution in which a Cu electrode made from a thick copper wire is immersed; the end of the wire is coiled. Part B is a specially constructed tube, the lower part of the two arms,





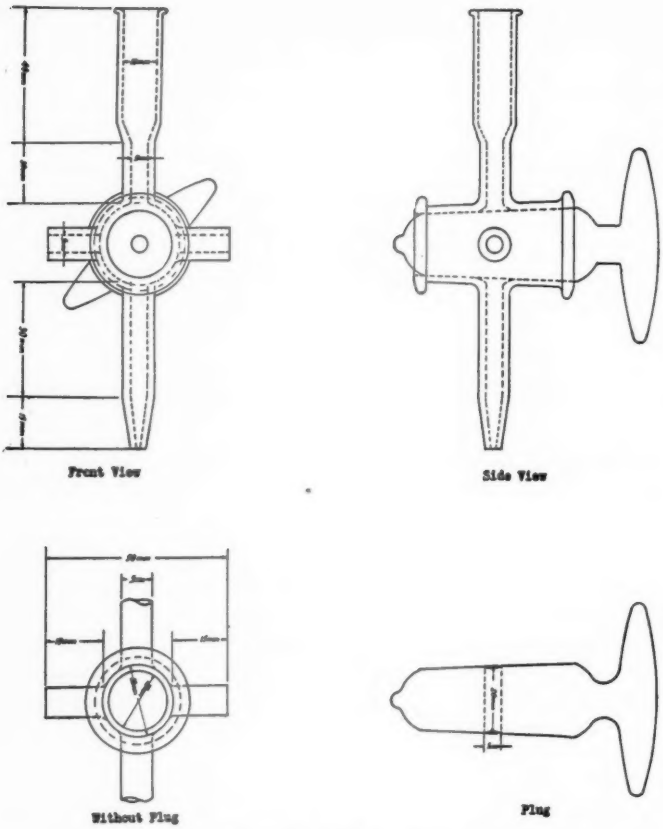


Fig. 8 - One of the Special Stopcocks or Cells of Apparatus Type C

as indicated in the figure, being filled with a 3 per cent sterile agar solution containing 3 per cent KCl; the wider arm is then filled with 10 per cent KCl solution, and the narrow arm with menstruum, both to the same height as determined by an etched line. Part C is an inverted U-shaped agar salt bridge connecting Part A with Part B. The agar is of the same composition as that used in Part B. It is filled with sterile agar by means of a pipette and kept in a vertical position until it is hard.

The "U" tubes are illustrated in Figures 1 and 4. The tubes (130x10 mm.) are connected with anode and cathode at each end of the series through their side arms. They offer ample distance for the microorganisms to travel from the median-receiving cell toward the anode or cathode, as the case may be, to prevent any possible secondary reaction.

The lower arm of the "U" tube has a pinch-cock and pipette leading to a sterile tube, thus allowing the contents to be removed for examination and culture when desired. The "U" tube also facilitates washing, filling, and emptying of the apparatus, and removing any air bubbles which may become trapped in the cells.

Macro-electrophoresis Apparatus Type B. This type is designed especially to study the electrophoresis of the larger microorganisms or particles and consists of a series of T-shaped cells (Figs. 1 and 4). The removal of samples from the individual cells and from the upper opening is accomplished by means of a pipette, instead of drawing from the bottom as in Type A.

In certain experiments, it is desirable to replace the receiving cell by a cross-shaped cell of Type A, or by a stopcock similar to the one of Type C. (See Fig. 5.) This will eliminate the three-way stopcocks and the central or receiving cell from the set-up.

Macro-electrophoresis Apparatus Type C. This type is esentially the same in principle as Type A, except that each four-arm cell and its isolating stopcocks are combined into a special cell which serves both purposes (Figs. 1 and 5). The individual cells consist of a specially designed stopcock with four outside arms and a plug with a two-way opening. The internal diameter of the opening of the plug is the same as that of the side-arms (about 5 mm.), thus presenting a uniform and constant diameter throughout the length of all the cells. When the stopcock plugs are turned horizontally, the cells are connected in a vertical position. The contents then flow into sterile test tubes which are attached to the cells by means of cotton plugs.

A piece of rubber tubing connecting a glass pipette to a cell may be used to receive the sample or the microorganisms the mobility of which is to be studied. The pinchcock is placed immediately above the glass pipette so that, if necessary, the rubber tubing can be manipulated by the pressure of the fingers to raise or lower the liquid in the plug and thus eliminate any air bubbles.

Macro-electrophoresis Apparatus Type D. This form which is a modification of Type A, consists of U-shaped cells with horizontal side-arms at the middle of U-arms (Figs. 1 and 6). The size and capacity of each cell can be increased as desired. This type can also be used for studying the transference number of ions.

RELATIVE MERITS OF TYPES A, B, C, AND D.

Types A, B, and D can be constructed in any laboratory, but the Type C apparatus is comparatively difficult to construct in an ordinary laboratory. Type C, having more uniform and definite diameter throughout the entire length of the unit cells, is preferable for the precise measurements of the rate of migrations of the samples to be studied. The individual cell in Type C has a capacity of about 10 to 20 drops. Although this feature may be disadvantageous in the study of colloidal solutions, it is distinctly advantageous in determining the velocity and securing the isolation filtrable viruses. Type D is designed to prevent the possibility of mechanical diffusion of the sample, and in this feature presents a definite advantage over the other types.

CALIBRATION OF APPARATUS.

The apparatus herein described is suitable for various purposes and can be standardized accordingly. The number of cells used, their distances from each other, and their internal diameters can be modified for the particular type of experiment contemplated.

THE OPERATION OF THE APPARATUS DURING A MEASUREMENT

Sterilization of the Apparatus. The assembled cells and stopcocks of Types A, B, C and D can be sterilized in an autoclave or by boiling, after first loosening the plugs of the stopcocks to prevent breakage due to expasion or contraction. The "U" tubes and the glass part of the non-polarizable electrodes can be steril-

ized in like manner or with dry heat. After sterilization the apparatus is assembled and the parts connected asceptically.

Preparation of Agar Jell and Non-polarizazle Electrodes. This jell is prepared by dissolving 3 per cent KCl (C.P.) and 3 per cent clean agar in redistilled water, and autoclaved at 15 pounds pressure for 20 minutes. It is cooled to about 60° C., a portion, usually 50 cc. per tube, is introduced with a sterile Pasteur pipette into the non-polarizable electrodes (Part B, Figure 2) to the level as shown in the diagram. At the same time several of the "U" tube bridges are filled with agar. After the solidification of the agar the wider tube of Part B (Fig. 3) is overlaid with 10 per cent KCl solution. The two parts of the non-polarizable electrodes, the one containing $CuSO_4$ and the other KCl solution, are connected by means of agar bridges.

Filling of the cells and the "U" tubes with Menstruum. The cells, with "U" tubes, and the parts of the narrow arms of the electrodes above the agar, are filled to the level of the etched line with sterile water or a given physiological salt solution. The liquid is poured directly into one of the vertical arms of the "U" tube, or through the narrow arm of a non-polarizable electrode, under sterile conditions if desired. The test tubes may be closed with sterile rubber stoppers instead of cotton, when a closed airtight system is necessary.

Care should be taken to prevent the introduction of air bubbles both in the cells and at the junctions of menstruum and agar. Any air bubbles trapped in the system are eliminated by slightly elevating one end of the apparatus, or by adding more fluid and removing a portion from the lower end of the "U" tube. The fluid level in all the cells is then equalized.

An electric current is next passed through the apparatus for a few minutes to determine whether the cells are properly connected. The current strength is adjusted by the series resistance and by a potentiometer. The former is used for coarse adjustment and the latter for fine adjustment.

Introduction of the Test-material into the Receiving Cell. The cell receiving the test-material may be located at the center, or near the anode or cathode, depending on the nature of the experiment.

After the isolation of the receiving cell the system is tested for leakage current; the curent is then shut off and the trial liquid or menstruum is removed. This operation is carried out in Types A, C and D by loosening the pinch-cock clamp attached to the lower end

of the receiving cell; in Type B the same object is accomplished by means of a pipette through the upper opening of the cell under sterile conditions. The removed menstruum is replaced with the test material by filling the cell up to the etched line. The connection of the receiving cell with the rest of the system is effected by the proper manipulation of the particular stopcocks, after which the current is adjusted and the time marked.

Electromotive Force. When apparatus Types A and B are filled with tyrode solution, 220 volts produce a current of about 10 milliamperes. When the same voltage is passed through Type C, about 15 will be registered. Inasmuch as most of the microorganisms can stand voltages and currents of this magnitude for several hours with no apparent injury (a current of 5 m.a. for 24 hours had no injurious effect on spirochetes of relapsing fever and on trypanosomes in Tyrode solution), the current can be increased with a corresponding shortening of time. Since this would require more than the standard 220 D.C. usually available in most laboratories, it would be necessary to use batteries or a high voltage iron rectifier operating from a 110-volt A.C. step-up transformer.

Microscopic Examination, Culture, and Inoculation Tests. After the current has been passed for the desired time, the stopcocks are closed. Another notation of the leakage current should be made again at this time and the circuit disconnected. The liquid from each cell is transferred to a test tube to be used for microscopic examinations, culture, and, whenever necsary, animal inoculation tests.

SUMMARY.

Four types of macro-electrophoresis apparatus are described in this paper. The relative merits of each are discussed along with their uses in isolating protozoa from bacteria and for studying the electrical charge and the rate of mobility of colloidal particles, microorganisms, and tissue cells. The apparatus is also suitable for determining the transference number of ions.

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STUDIES ON HYPERTENSION

II. The Effect of Spinal Anesthesia on the Blood Pressure of Hypertensive Patients. Its Possible Bearing on the Pathogenesis of Essential Hypertension*

RAYMOND GREGORY, E. L. LINDLEY AND HARRY LEVINE

In spite of the importance of essential hypertension as a cause of sickness and death and in spite of great effort which has been devoted to the subject in recent years as a result of the work of Goldblatt the etiology of this abnormality remains unknown. Attempts to define the etiology of essential hypertension have been directed principally from the following viewpoints: (a) the kidney: as a source of nervous reflexes and other mechanisms, (b) the vasomotor apparatus, (c) humoral mechanism—arising in the kidney or other organs.

REVIEW OF LITERATURE.

A. The Kidney as the Cause of Essential Hypertension.

Richard Bright first showed that renal disease may produce hypertension. Bright's ideas regarding the relation of diseases of the kidney to high blood pressure were deduced from his observation of the high degree of correlation between renal disease and cardiac hypertrophy in the absence of intrinsic cardiac disease. His clinical and pathological observations founded the school which believes in the etiological relationship between renal disease and hypertension. This concept has been contributed to by other important workers in the field of renal diseases (Jores, Volhard and Fahr). The validity of the hypothesis of the renal origin of hypertension may have been an impetus to Goldblatt (1934, 1937) whose work showed so conclusively that the kidney may be the origin of pathological physiological processes which cause hypertension. Goldblatt's results have been confirmed and extended. These experiments have further directed attention to abnormalities of the kidney as a cause of hypertension. The original studies of Goldblatt (1934) and co-workers focused attention on the kidney as the organ which may give rise to hypertension

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under certain conditions. It remained for Goldblatt and others, particularly Houssay and Braun-Menendez, to elucidate the mechanism by which renal ischemia produces hypertension.

The role played by the nervous system in general and particularly by the nerve supply of the kidneys in experimental hypertension due to renal ischemia has been thoroughly investigated. Goldblatt, Gross, and Hanzal were unable to lower the blood pressure of dogs made hypertensive by renal ischemia by resection of the splanchnic nerves; nor were they able to prevent it by splanchnic resection prior to the production of renal ischemia. Goldblatt and Wartman found that section of anterior spinal roots from the sixth thoracic to the second lumbar inclusive did not prevent or reduce hypertension produced in dogs by partial constriction of main renal arteries. Page (1935) and Collins observed no change following section of the renal nerves in the blood pressure of experimental hypertension caused by renal ischemia in dogs. Even total thoracic and abdominal sympathectomy with cardiac denervation failed to prevent the development of or to lower the elevated blood pressures produced by renal ischemia (Freeman and Page). Blalock and Levy and Glenn, Child and Heuer showed that the nerve supply of the kidney was not essential to the development of hypertension caused by renal ischemia by producing hypertension in dogs with ischemia of a transplanted kidney. These results have been adequately confirmed and it appears that the nerve supply of the kidney and the functional integrity of the sympathetic nervous system are not essential to the production or maintenance of hypertension due to renal ischemia. The results of Dock and Rytand are not in agreement with this, however. They found the brain and cord essential to the maintenance of experimental renal hypertension in rats. They concluded that the pressor substance present in the plasma of rats with renal hypertension has no peripheral vasoconstrictor action, but acts through the vasomotor center. Pithing the cord may be criticized on the grounds that this results in such a poor physiological preparation that results with such a preparation would not be reliable. They showed, however, that epinephrine and pituitrin, known to act in the periphery,

continued to produce transient rises in pressure in their hypertensive rats after pressures were reduced by pithing.

Goldblatt (1937) stated further that failure of surgery on the sympathetic nervous system to alter or prevent the development of hypertension in the dog with renal ischemia tends to minimize the role of the vasomotor apparatus of all parts of the body except the kidney so far as the cause of hypertension is concerned. If this be true, the question should be raised concerning the mechanism by which the kidney initiates the elevation of blood pressure. By implication, Goldblatt apparently believes that vasomotor impulses to the kidney are important in the genesis of hypertension. If this be so, what causes the abnormal vasomotor function to the kidney? Goldblatt (1937) stated also that failure of various surgical procedures on the nervous system to lower the blood pressure in experimental hypertension does not support the operations performed on human beings with hypertension; but it does not necessarily disprove, however, the reports of beneficial effects obtained by these procedures in some cases of human hypertension. He emphasized that sympathectomy can not influence the silver clamp on the renal artery which has caused the ischemic kidney to produce a humoral pressor substance. He also emphasized, however, the possibility that constricted renal arterioles may produce renal ischemia, and thereby, a pressor substance in the kidney; and that this arteriolar constriction might be relaxed by interruption of vasomotor impulses to the kidney with resulting correction of renal ischemia producing the hypothetical pressor substance. In this regard the work of Weeks et al should be mentioned. They found that unilateral splenorenopexy in dogs caused elevated blood pressures produced by renal ischemia to return to normal. They attributed this effect to the correction of renal ischemia by a better collateral blood supply around the tubules. They found, however, that omentorenopexy produced only a temporary fall in dogs with hypertension due to renal ischemia. Goldberg, Rodbard, and Katz reported that increasing the collateral circulation to the kidney by decapsulation and transplantation of the kidney to a muscle bed led to a temporary fall in the blood pressure in dogs with hyper-

tension due to renal ischemia. When a normal dog had this performed beforehand, it did not interfere with the development of hypertension by subsequent partial occlusion of the renal artery. Katz et al explained the failure of this procedure to lower the blood pressure to probable compression of the kidney by scar tissue. This would not appear to be the case inasmuch as the blood pressure returned to previous levels within such a few days after operation. Undoubtedly scar tissue resulted from the splenorenopexy reported by Weeks et al but the blood pressure fell to normal levels. Regardless of the mechanism involved, Katz stated that operations designed to increase the collateral circulation to the kidney are unjustified as a means of treatment of hypertension of any sort, even the so-called "renal" hypertension.

Page and Heuer (1935) found the arterial blood pressure unchanged by denervation of the kidneys in one case of essential hypertension. They concluded that this showed that nervous impulses originating *in* the kidneys did not share in the maintenance or genesis of hypertension. If this be true, it seems equally true that nerve impulses *coming to* the kidney must not have shared in the genesis of the hypertension unless it is assumed that too much organic damage had already been done by the time denervation was done. This appears unlikely because this patient's renal function was normal before denervation, as indicated by the urea clearance and concentrating power of the kidneys.

Hypertension may also be produced in man by renal ischemia (Leiter, Freeman and Hartley, Leadbetter and Burkland, Boyd and Lewis, Oppenheimer, Klemperer and Moschkowitz, Nesbit and Ratliff, Blatt and Page, Barker and Walters, Bartels and Leadbetter, Boyd and Lewis, Longcope, and Butler). This is evidenced by the association of hypertension with lesions which partially obstruct the renal artery or intrarenal circulation and by the disappearance of hypertension following the removal of the ischemic kidney in some instances. A humoral mechanism of renal origin is accepted as the probable cause of hypertension in acute and chronic nephritis, chronic pyelonephritis, polycystic kidneys, renal amyloidosis, as well as in other less commonly encountered renal abnormalities such as

tumor masses which partially obstruct the renal artery (Fishberg).

The clinical and experimental work referred to appears to have established that renal vascular disease or abnormality may produce hypertension. Of this conclusion, there should be no valid doubt. This does not prove, however, that essential hypertension is produced in the same manner.

B. Vasomotor Aspects of Essential Hypertension.

Many earlier concepts of the etiology of essential hypertension have been based on this. While it is an obvious possibility, it has never been proved. The most that may be correctly said for it is that the cause of elevated blood pressure is compatible with vasoconstriction of vasomotor origin. Contributions to the possibility of a vasomotor etiology of essential hypertension have been made from diverse directions. From examination of pathological tissues, Gull and Sutton concluded that the diffuse vascular disease found in patients with hypertension is a primary pathological entity. Whether they were correct or not, their conclusions first stressed the non-renal origin of hypertension. Allbutt concluded that high blood pressure was primarily due to widespread vasoconstriction and that organic changes in smaller vessels were due to persistent hypertension, from his observations that organic arteriolar disease was not extensive enough to account for continued hypertension in some patients. The question of the cause of the vasoconstriction was not answered. Allbut did not believe that the kidneys played a significant role in the production of essential hypertension.

The failure of investigators to find renal disease in a small percentage of patients with hypertension has supported contentions that essential hypertension is primarily a generalized vascular disease and that organic renal pathology is secondary to the vascular disease. These observations apparently indicate that hypertension may exist without a persistent anatomical explanation for renal ischemia. If renal ischemia exists in these cases, it must obviously result from functional constriction of the renal blood supply. If this be the case, what produces the physiological constriction? If it is initiated by spasm, the possible role

of the sympathetic nervous system is an obvious, though not a proved, one.

There is difference of opinion regarding the frequency with which one meets with hypertension which is not associated with significant renal pathology. Herxheimer and Schulz said that renal arteriolosclerosis is found in 97 per cent of cases with hypertension. Bell and Clawson stated that 90 per cent of patients with hypertension with cardiac hypertrophy have renal arteriolosclerosis. This appears to be a significant fact. If only 90 per cent of hypertensive patients who have had the disease long enough to produce cardiac hypertrophy have renal arteriolosclerosis, it seems probable that many more than 10 per cent of the cases have early hypertension without renal vascular disease. In this connection, Kimmelstiel and Wilson stated that it must be borne in mind that less than 50 per cent of cases of essential hypertension show a completely diffuse arteriolosclerosis if mechanical obstruction to the circulation through the kidney is to be considered as a contributory factor to the hypertension. Jaffe reported an increase in the diameter of the afferent glomerular arteriole in the early phases of hypertension. Fishberg said that an intact kidney in essential hypertension is uncommon.

While the finding of hypertension unassociated with demonstrable renal pathology appears to be generally accepted, the most that one can conclude from it is that hypertension may be due to a non-renal cause. Any tendency to assume that this non-renal cause is therefore vasomotor in type is not justified and certainly not proved. The existence of essential hypertension without renal pathology does admit of the possibility that it might be due to vasomotor causes, however.

There are conflicting conclusions concerning the vasomotor apparatus in the production of essential hypertension. Older work emphasized the etiologic role of the vasomotor function in hypertension while much of the newer work is in disagreement with vasomotor etiology. Weiss and Ellis showed that the average resistance of the arteriolar system in patients with hypertension was twice that of normal subjects. The blood volume and cardiac output per minute were normal. While the demonstrated

vasoconstriction is possibly of vasomotor origin, there is no proof that such exists. Von Monakow reported that vasomotor centers are hyperirritable in hypertension. Hines and Brown obtained results with their "Cold Stimulation Test" that led them to conclude that hypertension is due to vasomotor irritability. They reported that 98 per cent of subjects with essential hypertension exhibited excessive reactions to cold. Particularly interesting, from the standpoint of the present study, is their finding that general anesthesia completely obliterated the response and spinal anesthesia, with sensory anesthesia to the nipple line or even the umbilicus, essentially prevented any vasomotor response to the application of cold. These results emphasize the possible importance of the central nervous system as a cause or sustaining mechanism in essential hypertension. Raab found that patients with essential hypertension responded to inhalation of carbon dioxide with rises of blood pressure several times greater than normal subjects. Normal responses were obtained in patients with hypertension due to nephritis. Mueller and Brown's observations of the extreme fluctuations of blood pressure during waking and sleeping supported the hypothesis of the vasomotor etiology of essential hypertension. Miller and Bruger confirmed the work of both Hines and Brown and Raab by finding that 76 per cent of patients with essential hypertension gave excessive responses to the cold-pressor test, while chonic nephritis with hypertension responded similarly to normal subjects. Their results were confirmed by Alam and Smirk. The difference in the reactions of essential and nephritic hypertensives to various tests by Raab, Miller and Bruger, and Alam and Smirk supports the possible difference in etiology of the two conditions. This is not agreed to by more recent workers, who favor a humoral mechanism for all types of hypertension (Prinzmetal and Wilson).

All published work does not agree that there is a difference in etiology of the two types of hypertension ("renal" and "essential"). Pickering concluded that hypertonus of blood vessels in essential and renal hypertension was not due to a nervous mechanism. He speculated on the possibility of a local excess of pressor or lack of depressor sub-

stances in the vessels or tissues surrounding the vessels. Prinzmetal and Wilson stated that hypertonus of blood vessels in all forms of hypertension studied was independent of vasomotor control. The conclusions of Prinzmetal and Wilson in coarctation of the aorta do not agree with those of Pickering. The former interpreted their results in coarctation of the aorta to indicate that the hypertension was of vasomotor origin. Pickering speculated that there was a congenital lack of growth of vessels as the cause of hypertension in coarctation of the aorta. The results and interpretations of Pickering and of Prinzmetal and Wilson are in agreement on essential and nephritic hypertension, and in complete disagreement regarding coarctation of the aorta. Are their methods as reliable as they believe?

The relation of vasomotor function to the etiology of essential hypertension has been studied to advantage by various surgical attacks on the sympathetic nervous systems of hypertensive patients in addition to those to which reference has been made on animals made hypertensive by renal ischemia. Adson and Brown, Page and Heuer (1935, 1937), Freyberg and Peet, and Craig and Brown have employed surgery on the sympathetic nervous system in the treatment of hypertension. All have claimed some success. Goldblatt (1937) stated that surgical procedures on the sympathetic nervous system which result in a lowering of blood pressure have only one thing in common—a denervation of the kidneys. He theorized that renal denervation may result in a better blood supply to the kidneys, the resulting decrease in ischemia possibly causing decreased production of renal pressor substance by ischemic kidneys. By the same right to theorize, one may argue that the loss of sympathetic impulses to the kidneys is not likely to result in a "corrective" amount of vasodilation of the renal arterioles unless such impulses initially caused the excessive vaso-constriction of the renal arterioles. Pickering (b) stated that the significance of the falls in blood pressure following section of splanchnic nerves and removal of lumbar sympathetic chains "is in doubt until we know the effects of similar operations in subjects with normal blood pressures." The effects of spinal anesthesia on normal human blood pressures, which

we are reporting, is the nearest to this of which we are aware.

It is theoretically conceivable that essential hypertension may be initiated by excessive vasomotor impulses and the persistently elevated pressure results in anatomical change in the renal arterioles that causes ischemia which produces a pressor substance in the kidney. Renal ischemia as the cause of experimental hypertension in animals and one which may operate in human beings has been discussed.

The literature is conflicting concerning the role played by the vasomotor function in the production of essential hypertension. While some abnormality of the vasomotor function is an attractive possibility, and the literature cited above is partially in conformity with this possibility, no conclusive proof is available that this is the cause of essential hypertension.

C. Humoral Mechanism for Production of Hypertension.

Certain abnormalities of the adrenal medulla and the adrenal cortex are known to be associated with a hypertensive state in patients. Surgical removal of these abnormalities usually causes the hypertension to return to normal levels. It is not believed, however, that these conditions are the cause of "essential hypertension" (Fishberg).

The work of Goldblatt et al (1934), confirmed and extended by many, has directed attention to the humoral mechanism involved in the production of experimental hypertension in animals by renal ischemia. Kohlstaedt, Helmer and Page (1938, 1940), and Plentl and Page (a, b) have made significant contributions to the problem of a specific humoral substance which may be involved with work on "angiotonin." Goldblatt (1937) has also suggested, on the basis of experimental evidence, that the adrenal cortex and pituitary may play a part in the development of experimental hypertension produced by renal ischemia. This has been confirmed by Blalock and Levy. This effect may be due to the general systemic requirements of these substances for health rather than to any specific relationship. Although newer experimental evidence supports a humoral mechanism as a possible cause of hypertension, and the clinical evidence previously mentioned supports the belief that hypertension due to renal

ischemia does occur in human beings, the literature is confusing regarding attempts to isolate a pressor substance from the blood or tissues of patients with hypertension.

Much effort has been given to study of the humoral substance which is probably the cause of experimental hypertension due to renal ischemia and which may possibly be the cause of essential hypertension. Kohlstaedt, Helmer and Page (1938, 1940), and Plentl and Page (a, b) reported that the substance produced by the ischemic kidney in experimental hypertension and probably by the patient with essential hypertension is renin which is activated by a globulin fraction of blood plasma, called "renin-activator," to form "angiotonin." Tigerstedt discovered renin in the normal kidney many years ago. Page and his collaborators have crystallized angiotonin. They have also studied a purified renin and renin activator and concluded that the activiation is enzymatic (Plentl and Page). Contrary to an earlier publication, they concluded recently (1943) that renin is the enzyme and "renin activator" is the substrate.

The literature is conflicting regarding pressor compounds in the blood of hypertensive patients or in the blood of animals made hypertensive by renal ischemia. Danzer, Brody and Miles reported that the blood of patients with hypertension contained a pressor substance not found in rabbit's blood or in the blood of patients with normal blood pressures. Curtis, Mancrieff, and Wright duplicated the work of Danzer et al but found no pressor substance in the blood of patients with hypertension. Both investigations may be criticized because blood of human beings was injected into an animal of another species, the cat. Bohn claimed that he had demonstrated a pressor substance in an alcoholic, protein-free extract of citrated blood from "pale" hypertensives (nephritics), but that similar extracts of blood of both normal individuals and "red" hypertensives (essential hypertension) produced a fall in blood pressure. He, too, injected extracts of human blood into an animal of a heterologous species. De Wesselow and Griffiths were unable to confirm Bohn's results. They could adduce no evidence of a pressor substance in the blood of patients with essential hypertension. Ultrafil-

trates from plasma showed no effect with the exception of a slight pressor effect produced by an ultrafiltrate of blood from a patient with chronic glomerulo-nephritis with slight renal failure. Aitken and Wilson were also unable to confirm the claim of Bohn that bloods of "pale" hypertensive patients contained a pressor substance. Page (1935, b) reported that blood and cerebrospinal fluids of normal individuals and ascitic fluids contained a pressor substance. He could not demonstrate any increase of this pressor substance in the blood or cerebrospinal fluids of patients having hypertension. Interestingly, he observed that the medulla and spinal cord were essential for the production of this pressor effect. Fasciolo, Houssay, and Taquini stated that blood from the renal vein of a dog's ischemic kidney contains more pressor substance than blood which had passed through a dog's normal kidney. They used a perfusion technique on the South American toad. Using frogs, bullfrogs, and toads from the southern part of the United States of America, Mason and Rozzell were unable to confirm the results of Houssay and co-workers. The use of such widely different species as the dog and the frog is again open to criticism. Page (1940), using the perfused rabbit's ear, stated that "since vasoconstriction occurs under the same experimental conditions with plasma from both hypertensive patients and dogs, this is considered cogent evidence in favor of the view that the chemical mediator of both is similar and is possibly angiotonin."

While the methods used are perhaps open to question on the grounds mentioned, the results of injecting blood, plasma, or extracts of blood and of plasma from hypertensive patients into other animals have failed to demonstrate conclusively the presence of a pressor substance in the blood hypertensive patients.

The possible production of a pressor substance by hypertensive patients and animals has been studied with extracts of kidneys. Prinzmetal and Friedman reported considerable variation in the results obtained from injecting extracts of kidneys from patients with normal blood pressures and from patients with high blood pressures. Although there was overlapping, the average rise of blood pressure from extracts of the former was twelve milli-

meters of mercury while the average rise from the latter group was twenty-eight millimeters of mercury when identical amounts of the two different extracts were injected into dogs. They also studied extracts from the kidneys of dogs in which one kidney was made ischemic. The other kidney was not disturbed. In eleven of fourteen dogs the extract from the ischemic kidney contained a greater amount of pressor substance than an extract from the normal kidney. Harrison, Blalock and Mason obtained similar results with dogs made hypertensive by both renal ischemia and unreteral ligation. Landis found no evidence that extracts of kidneys from patients with benign hypertension or chronic glomerulonephritis contained any greater amount of pressor substance than did extracts of normal kidneys. Extracts from kidneys of patients with malignant nephrosclerosis produced slightly greater pressor effects.

Published evidence indicates that ischemic kidneys of hypertensive dogs contains a greater amount of pressor substance than do normal kidneys of dogs. An excessive amount of pressor substance in the kidneys of hypertensive patients has not been demonstrated. This may be due to post mortem destruction before or during the preparation of the extract. The evidence concerning a pressor substance in the blood of hypertensive patients or hypertensive dogs is still too conflicting to permit of any conclusions.

An important contribution is the report of Pickering (a), who observed no effects on the blood pressures of anemic patients as a result of transfusing them with as much as 600 cc. of blood from hypertensive patients. Pickering raises an obvious criticism that a pressor substance may be present in the blood but that it may be quickly destroyed or diluted with resulting lack of pressor effect. He believed, however, that the methods he used controlling the lapsed time properly answer this criticism. He concluded that his results are opposed to the idea that essential hypertension is due to an excess of pressor substance in the circulating blood.

Convincing evidence has been adduced that hypertension produced by renal ischemia in animals is due to a circulating pressor substance formed in the ischemic kidney. There is no convincing proof, however, that essential

hypertension is due to or associated with the circulation of a pressor substance in the blood of such patients. In summary, it has been stated "the results of various experiments indicate that this type of experimental hypertension (*renal ischemia*) is due primarily to a humoral and not to a nervous mechanism initiated by the ischemia of the kidneys" (Goldblatt, 1937). The literature is in complete agreement with this. It must be emphasized, as Goldblatt has done, that while this *may* also be the cause of essential hypertension; and, as Prinzmetal and Wilson contend, of all types of hypertension, the conclusion is valid only so far as the hypertension associated with proved renal ischemia is concerned.

Study of the effect of spinal anesthesia on the levels of blood pressures in patients with essential hypertension have produced data which do not support a humoral mechanism as the cause of essential hypertension.

METHODS.

Twelve patients with normal blood pressures were subjected to spinal anesthesia for controls. Procaine hydrochloride was used according to the method described by Maxson. Twenty patients having a clinical diagnosis of essential hypertension were similarly studied twenty-two times as the experimental group. Usually 150 milligrams of procaine hydrochloride dissolved in three cubic centimeters of cerebrospinal fluid was employed. In a few instances, 100 milligrams of procaine hydrochloride in two cubic centimeters of spinal fluid was administered. Immediately after the rapid subarachnoid injection of this solution, the patient was placed flat on the back. Observations begun before the spinal anesthesia for control levels of blood pressures, sensory levels, and the motor capacity for voluntary movement in the lower extremities were continued. These observations were made at five to ten minute intervals for two or more hours or until the blood pressures had effectively returned to the control levels.

Although it is difficult to see how the subarachnoid injection of procaine hydrochloride could influence the peripheral vasomotor apparatus or the capacity of the vessel walls to constrict, it was considered desirable to test the capacity of the vessels to react to a pressor substance known

to act in the periphery. Accordingly, during the period of fall in the blood pressures of hypertensives due to spinal anesthesia, and often at the lowest level of the fall, varying amounts of epinephrine hydrochloride were injected subcutaneously, intramuscularly, or intravenously.

Attention is directed to a few patients (V. D., M. T. and A. K.), in whom there was retching and vomiting when the blood pressure had fallen to the lowest levels due to spinal anesthesia.

RESULTS.

The blood pressure levels before and during spinal anesthesia on the group of patients with normal blood pressures are summarized in Tables I and II and Figures I and II respectively. Control levels of blood pressure and the experimental levels during spinal anesthesia on the group of patients with hypertension are summarized in Tables III and IV and Figures III and IV respectively. The average blood pressures at each time interval for both the normal and hypertensive group during both control and experimental periods may be found at the bottom of the respective tables.

Figure V summarizes the average blood pressures of ten patients with normal blood pressures before and during spinal anesthesia. Figure VI presents the same data for twenty patients with hypertension. In Figure VII is tabulated the average blood pressures of ten patients (E. W., L. C., J. M., J. B., M. C., L. W., W. G., V. D., O. B., A. K.) with essential hypertension who showed the greatest falls in blood pressure during spinal anesthesia. Reference to Tables I and II and Figures I and II show that there was a slight fall in the blood pressure of several patients with normal blood pressures during spinal anesthesia (J. F., D. R., T. M.). The blood pressures in the group with normal pressures remained essentially the same during the period of spinal anesthesia as during the control period. Reference to the average blood pressures of the normal group in Tables I and II and to the graphic representation of these averages in Figure V shows that there is little if any significant difference in the pressures before and during spinal anesthesia. The maximal average fall in pressures during spinal anesthesia was only seven millimeters

of mercury systolic and six millimeters of mercury diastolic. The average fall for the first hour was four millimeters of mercury systolic and four millimeters of mercury diastolic.

Reference to Tables III and IV and Figures III and IV indicate the marked individual as well as average drops in blood pressures due to spinal anesthesia in patients with hypertension. Three of the twenty-two experiments on twenty patients resulted in a maximal fall of only eight millimeters of mercury systolic pressure and eight to twelve

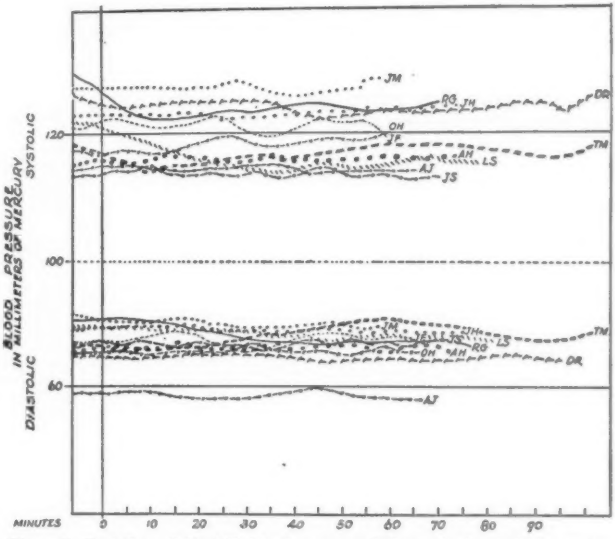


Figure I. Systolic and diastolic blood pressures before spinal anesthesia on ten patients with normal blood pressures.

millimeters of mercury diastolic pressure in one (L. J.), fourteen millimeters of mercury systolic in another (J. A.) and sixteen millimeters of mercury systolic in the third (A. J.). In spite of the slight and possibly insignificant fall in pressure in these three patients, it was as great in one and twice as great in two others as the maximal average fall in pressure which occurred in the normal group during spinal anesthesia. It is to be noted that initial blood pressures in these three patients were not high compared to the others. All the others showed moderate to extreme

drops in blood pressure. Reference to Table IV and Figure VI shows the average marked fall in systolic and diastolic pressures during spinal anesthesia in patients with hypertension. Particular attention is directed to Table IV and Figures IV, VI and VII that there may be noted the rapidity with which the blood pressures of patients with

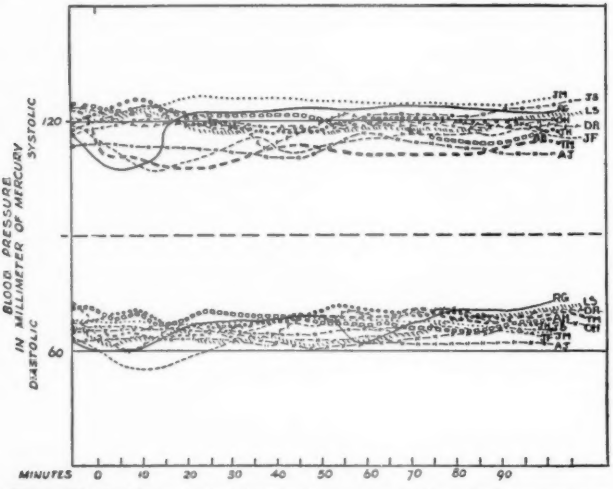


Figure II. Systolic and diastolic blood pressures during spinal anesthesia on ten patients with normal blood pressures represented in Figure I. The induction of spinal anesthesia occurred five to ten minutes before zero time.

hypertension fall following the induction of spinal anesthesia.

In Table V are summarized the effects of epinephrine when injected at the time of the fall in blood pressure due to spinal anesthesia in patients with hypertension.

Table VI presents data pertaining to effects of vomiting on blood pressures of three patients whose pressures were at the lowest levels of the fall produced by spinal anesthesia. The average rise in blood pressure due to four vomiting episodes in three patients was sixty millimeters of mercury systolic and forty millimeters of mercury diastolic.

DISCUSSION OF RESULTS.

This study has shown that there is a difference in the effects of spinal anesthesia on the blood pressures of pa-

tients with normal blood pressures and those with hypertension. The mechanism by which spinal anesthesia produces the marked fall in blood pressure of patients with hypertension is most likely, if not certainly, the functional blocking of vasomotor fibers. If this be the explanation, it appears logical to conclude from the data presented, that the functional integrity of the sympathetic nervous system is essential to the maintenance of the elevated blood pressure of hypertension. Quite at variance with much of the

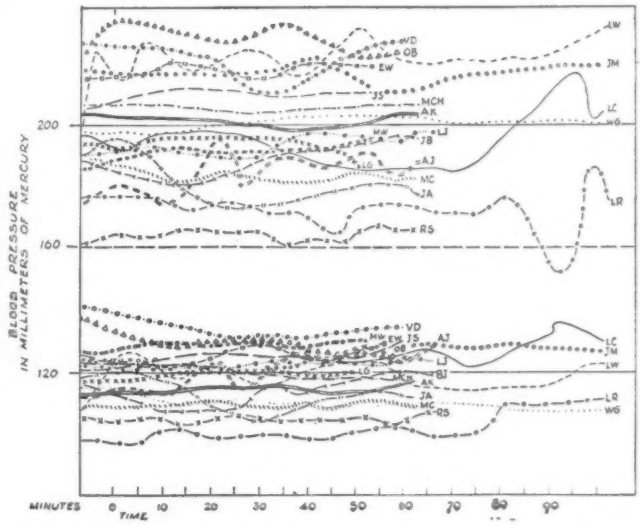


Figure III. Systolic and diastolic blood pressures on twenty patients with essential hypertension before spinal anesthesia.

literature, we believe that the profound depressor effect of spinal anesthesia on the level of hypertensive blood pressures indicates the importance of the vasomotor function in the genesis and maintenance of the elevated pressures of hypertensive patients.

Proponents of the renal humoral mechanism of the genesis of essential hypertension may argue, as does Goldblatt and collaborators (1937) regarding surgery on the sympathetic nervous system for treatment of hypertension, that interruption of the function of the vasomotor apparatus by spinal anesthesia reduces the blood pressure by

dilating the renal arterioles, thereby improving the circulation to the kidney, with resulting decrease in renal ischemia and production of less pressor substance by the kidneys.

It seems a fundamental fault of this hypothesis that it assumes the blood flow through the kidney is necessarily increased in hypertensive patients as a result of interruption of sympathetic impulses. We are not aware that this has been proved. Gregory, Lindley, and Levine have presented data from a study of the urea clearance of twenty hypertensive patients which indicate that renal function may suffer greatly as a result of spinal anesthesia in patients with essential hypertension. Yet there was a marked fall in the blood pressures of these patients resulting from the spinal anesthesia. It seems unlikely that the fall in blood pressure during spinal anesthesia in patients with essential hypertension is due to increased circulation through the kidney when a reduction in renal function has been demonstrated at the same time. A more likely explanation, the interpretation we have made, is that spinal anesthesia first causes blood pressures to fall and renal function falls in consequence. In this connection, we call particular attention to patients J. M. and V. D. in Tables III and IV. In patient J. M. the systolic blood pressure fell 178 millimeters of mercury and the diastolic pressure fell eighty millimeters of mercury as a result of spinal anesthesia. Yet the renal function was much impaired before the period of spinal anesthesia as evidenced by a urea clearance of thirty-eight per cent and a blood urea nitrogen of twenty-nine milligrams per 100 cubic centimeters of blood. The urea clearance fell further to a level of eleven per cent during the greatest fall of the blood pressure and, as was shown by Gregory, Lindley, and Levine, the urea clearance improved as the blood pressure rose, rather than decreased as might be expected from the hypothesis of Goldblatt (1937). In patient V. D., the urea clearance was fifty-nine per cent before spinal anesthesia. It fell to twenty-two per cent during the maximal fall in blood pressure and again rose to forty per cent with rise in blood pressure during the second hour of the test. In spite of initially impaired renal function and its further decrease during spinal anesthesia, blood pressure fell from 250/144

to 112/92 as a result of the spinal anesthesia. We not only wish to point out, as we have previously done (Gregory, Lindley, and Levine), that the renal function and blood pressure fall and rise together as a result of the effects of the spinal anesthesia but we also wish to emphasize in regard to patients J. M. and V. D. that they had serious impairment of renal function before the spinal anesthesia. J. M. even had a slight nitrogen retention of twenty-nine

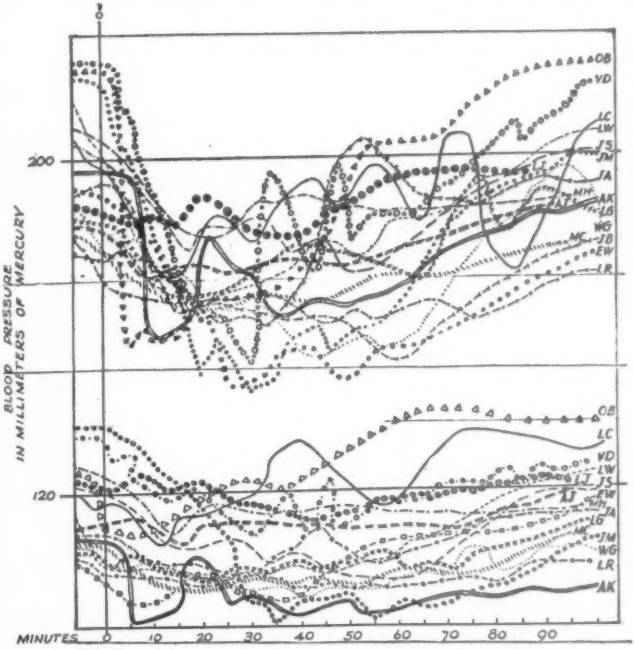


Figure IV. Systolic and diastolic blood pressures on the same twenty patients represented in Figure III during spinal anesthesia. Spinal anesthesia was induced at zero time. Attention is directed particularly to the precipitate drops in blood pressure following spinal anesthesia. The sudden and transient elevations which may be noted, such as in the systolic blood pressure of V. D., were due to vomiting or to the injection of epinephrine in a few instances.

milligrams of blood urea nitrogen per 100 cubic centimeters of blood. We assume that impairment of renal function was due to irreversible organic glomerular disease, inasmuch as we know of no evidence that impairment of renal function can be produced in patients with essential hypertension by spasm of renal blood vessels. Congestive

failure was not present as shown by normal venous pressures. In spite of this degree of organic renal disease, spinal anesthesia produced a profound fall in the blood pressures of these two patients (J. M. and V. D.). We are unable to conceive the likelihood that spinal anesthesia produced the great fall in blood pressures which occurred in these two patients with marked organic renal disease within a few minutes after induction of spinal anesthesia

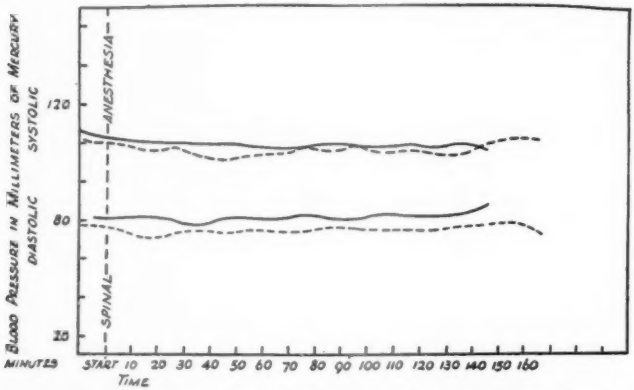


Figure V. The unbroken curves represent the average systolic and diastolic blood pressures on ten patients with normal blood pressures. The other pertinent data concerning the blood pressures of these patients may be found in Table I and Figure I. The broken line curves are average systolic and diastolic blood pressures on the same ten patients during spinal anesthesia. The pertinent data from which these curves were derived may be found in Table II and Figure II.

by the process postulated by Goldblatt with regard to surgery on the sympathetics, namely, by improvement of the circulation through the kidney and resulting decrease of renal ischemia and decrease in production of a pressor substance.

We are opposed to the consideration of any mechanism for the fall in the blood pressure of patients with hypertension associated either with surgery on the sympathetic nervous system or the effects of spinal anesthesia other than interruption of vasomotor impulses. The other two possibilities of either decrease in cardiac output or decrease in viscosity of the blood could not become operative, almost certainly, in the short time during which the blood pressures of hypertensive patients may fall precipitately

following the induction of spinal anesthesia. Reference has already been made to the conclusions of Weiss and Ellis that essential hypertension is due to vasoconstriction. We believe the data we have presented agree with their conclusions. We further believe that our data substantially support the likelihood that the vasoconstriction is of vasomotor origin.

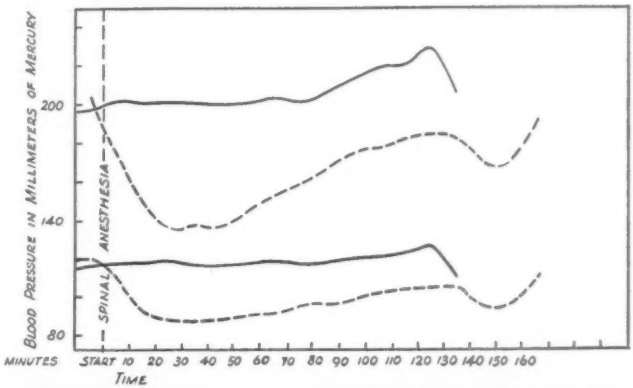


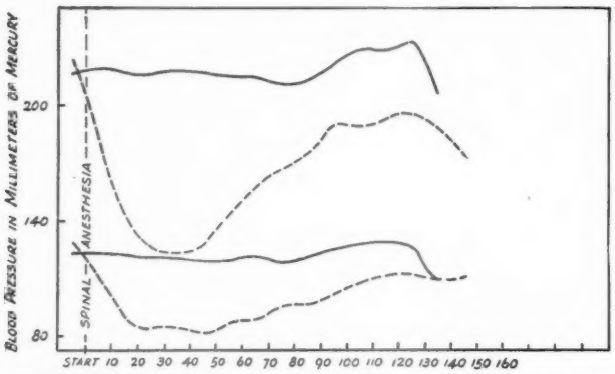
Figure VI. Solid line curves represent the averages of the sytolic and diastolic blood pressures on twenty patients with essential hypertension before induction of spinal anesthesia. The broken line curves represent the averages of the sytolic and diastolic blood pressures on the same twenty patients during a period of spinal anesthesia. The pertinent data from which these curves are derived may be found in Tables III and IV and Figures III and IV respectively.

When vomiting occurs during the period of low blood pressure caused by spinal anesthesia, the blood pressure rises. We interpret this to show that the heart still responds to the increased return flow to the right heart caused by "squeezing" of blood out of the abdomen by the vomiting act. It seems unlikely, therefore, that the fall in blood pressure during spinal anesthesia is due to interference with venous return or the heart's capacity to respond normally to venous return.

The rapidity with which blood pressures of hypertensive patients fall following induction of spinal anesthesia has been referred to and commented upon. It seems probable that comparison of this rate of fall with that which occurs in animals and man following removal of ischemic kidneys or release of constricting clamps on renal arteries might be fruitful with regard to whether essential hypertension and experimental hypertension are produced by the

same mechanism. The literature includes important relevant data.

Goldblatt (1937-38) reported the effects on the blood pressure of removing one or both clamps after hypertension had been produced in six dogs by renal ischemia. Detailed graphic records of three animals were reported. In Dog No. 1-40 a blood pressure of 285 millimeters of mercury developed in about twelve days following separate clamping of both kidneys. Following release of the clamp on one renal artery, thirty-six to forty days were required for the blood pressure to fall to normal. The blood pressure was still about 200 millimeters of mercury twenty-four days after release of the clamp. It is emphasized that one renal artery was still partially constricted. Dog No. 2-67 developed hypertension after partial constriction of the renal arteries. A number of days elapsed before the blood pressure fell to pre-operative levels and twelve days elapsed before the pressures fell to the lowest level following the removal of one ischemic kidney. Dog No. 2-50 was made hypertensive by partial constriction of the right renal artery *only*. This kidney was later removed. Twenty to twenty-four days were required for the blood pressure to return to normal level after nephrectomy. The left renal artery was then partially occluded, following which about


BLOOD PRESSURE IN MILLIMETERS OF MERCURY
200
140
80
SPINAL ANESTHESIA
START 10 20 30 40 50 60 70 80 90 100 110 120 130 140 150 160

Figures VII. The solid line curves represent the averages of the blood pressures on ten patients with essential hypertension (E. W., L. C., J. M., J. B., M. C., L. W., W. G., V. D., O. B., A. K.) before the induction of spinal anesthesia. The broken line curve shows the average blood pressures of the same ten patients during a period of spinal anesthesia. The date obtained from which these curves were constructed may be found in Tables III and IV.

forty-eight days were required for the blood pressure to rise from 140 to 300 millimeters of mercury. In general, this is representative of the rate at which blood pressures rose following partial constriction of the renal artery and fell following the release of the constriction or nephrectomy. Blalock and Levy also noted that at least a number of hours were entailed in the development of hypertension following production of renal ischemia as well as for the decline of blood pressure following correction of renal ischemia. At least five to seven hours elapsed after clamping of a renal artery before the blood pressure began to rise. There was always an elevation present the next day, but a maximal rise ocurred only after several days. Following the removal of an ischemic kidney under local anesthesia, these workers stated that the elevated blood pressure "began to decline in an hour or two" and in most instances approached closely the control level in six to twelve hours. While the time required for the blood pressure to rise and fall after production and correction of renal ischemia respectively in Blalock's animals was shorter than that observed by Goldblatt, both sets of data indicate that rise and fall of blood pressure was a much slower matter than that which we have observed with hypertensive patients in relationship to the effects of spinal anesthesia. The results of Rodbard and Katz are in substantial agreement. In dogs with hypertension due to renal ischemia they found that removal of an ischemic kidney, with a remaining normal kidney, resulted in a return of blood pressure to normal levels in six hours; while the removal of an ischemic kidney, with no kidney left, resulted in a return to normal levels of pressure in about thirty hours. They interpret their data to show that the chemical mediator of hypertension due to renal ischemia is destroyed, neutralized or otherwise eliminated at a rapid rate only in the presence of normal kidney tissue. By "rapid rate," they appear to mean something in the neighborhood of six hours. Friedman, Jarman, and Klemperer observed that many days were required after nephrectomy for the blood pressure to fall in rats made hypertensive by unilateral cellophane perinephritis. In Rat No. 89, thirty to forty days were required. Work on ani-

mals thus seems to indicate that the humoral substance responsible for elevation of blood pressure due to renal ischemia is not destroyed or excreted in a few minutes—but rather in a matter of hours or days—and is, therefore, probably not responsible for essential hypertension. If rapid fall of blood pressure associated with spinal anesthesia is due to cessation of production of a pressor substance by the kidney, then that which is present in the body at the time production ceases must be destroyed or excreted almost instantaneously in order to reconcile this with Goldblatt's ideas. We believe, therefore, that essential hypertension is not due to a circulating pressor substance; or if it is caused by a pressor substance, it is not the same pressor substance which causes hypertension of renal ischemia.

In order that this may not be criticised on the basis of comparison of duration of action of this hypothetical substance in animals and in man, we have sought information on this point in man from the literature. It is conceivable that the duration of action of a substance in a dog and in man may be different.

Barker and Walters observed a forty-two year old male with an initial blood pressure of 232/135. With rest in the hospital, his pressure varied between 170/120 and 200/140. Following a diagnosis of unilateral pyelonephritis with contracted kidney, nephrectomy was performed. The remaining kidney was presumably normal. Three hours postoperatively the blood pressure was 230/140. Eleven days were required after operation for the blood pressure to decline gradually to 140/100. Bartels and Leadbetter reported a case of unilateral, noninfected hydronephrosis treated by nephrectomy following which the blood pressure returned to normal only gradually over a period of many weeks. Oppenheimer, Klemperer, and Moschkowitz reported a nephrectomy on a patient with severe unilateral pyelonephritis and hypertension who had a "gradual decline" of pressure over a period of several days. Nesbit and Ratliff reported seven cases of hypertension associated with unilateral nephropathy. In only one of the cases is mention made of the time required for the blood pressure to fall after nephrectomy. They report in their case No. 4 that

the "blood pressure gradually fell" to 140/90 on discharge.

The rapidity with which blood pressures of patients with hypertension fall following surgery on the sympathetic nervous system compares closely with the quick fall of blood pressures due to spinal anesthesia in patients with hypertension in the few instances we have found in the literature. Adson and Brown reported the case of a patient who had a pre-operative blood pressure of 228/156. Early in the operation of section of the anterior nerve roots, sixth thoracic to first lumbar inclusive, the blood pressure rose to 250/178. This was thought to be due to the ether. Subsequently "during the operation" the blood pressure fell to 80/50. They did not believe this was due to shock. Page and Heuer (1937) reported effects of section of the lower thoracic and sometimes first and second lumbar anterior nerve roots in twenty patients with essential hypertension. Some statement was made regarding time required for blood pressure to fall following section of the roots in seven patients. In Patient No. 2 the blood pressure fell from 195/140 to 120/70 "during the operation." Patient No. 3 showed a fall in blood pressure from 180/122 to 100/70 "on the day of operation." Patient No. 4 had a fall of pressure from 190/130 to 110/70 "during the operation." Patient No. 7 had a fall of pressure from a pre-operative level of 182-212/108-132 to 90/60 "immediately after the operation." The blood pressure of Patient No. 8 fell from 210/130 to 90/40 immediately after the operation. Patient No. 9 died during the operation, and during the latter part of the operation "the blood pressure varied alarmingly." Patient No. 13 had an average pre-operative level of 270/100, the blood pressure fell to 100/70 "shortly after operation."

There seems to be, therefore, a close agreement in the time required for the blood pressures of animals and patients who have a "Goldblatt type" of hypertension to fall to normal following either nephrectomy or correction of renal ischemia. This varies from six to twelve hours to several days. There is also close agreement in the rapidity with which the blood pressures of patients with essential hypertension fall during spinal anesthesia and following section of the lower dorsal and upper lumbar anterior spinal

nerve roots. The required time is short—a matter of minutes. All this suggests either that "Goldblatt type" of hypertension and essential hypertension are due to different causes, or, if they are due to the same cause, that sympathetic block or section does not lower the blood pressures of essential hypertension by relieving renal ischemia and thereby decreasing the production of a pressor substance.

Reports on man appear to indicate that the humoral substance concerned with renal hypertension is slowly excreted or destroyed. This is a further point in favor of the belief that hypertension in dogs produced by the method of Goldblatt and that found in man associated with certain renal diseases which interfere with renal circulation may be due to the same mechanism. The slow rate at which blood pressures rise and fall respectively following production and correction of renal ischemia in animals and man compared to the rapidity with which blood pressures of patients with essential hypertension fall and rise respectively with induction and wearing off of effects of spinal anesthesia, as well as following section of sympathetic nerves in some cases, points to a lively difference in the cause of hypertension in renal ischemia and in essential hypertension.

Goldblatt's theory that a drop in blood pressure following surgery on the sympathetic nervous system or spinal anesthesia is due to increase in the circulation of the kidney and a decrease in the amount of pressor substance formed by the kidney assumes, in the light of the data we have presented, that the pressor substance formed by the ischemic kidney is almost instantaneously excreted or destroyed. It is theoretically possible for the assumed pressor substance to be quickly destroyed. On the other hand, the literature referred to indicates that the humoral substance which causes the "Goldblatt type" of hypertension does not fall for a number of hours or days following the removal of the ischemic kidney or the release of the clamp producing the ischemia. The results of our study show that the blood pressures in hypertensive patients fall rapidly, even precipitately, due to the effects of spinal anesthesia. It seems justifiable to believe, therefore, that essential hypertension is probably not due to the same pressor

substance that causes the "Goldblatt type" of hypertension, if it is, indeed, due to a humoral mechanism of any sort.

In the light of the slow rate of excretion or destruction of the humoral substance producing hypertension associated with renal ischemia and the data we have presented which show the rapid rate of fall of blood pressure in patients with essential hypertension during spinal anesthesia, our observations of the effect of epinephrine during the interval that the blood pressures of hypertensive patients have been depressed by spinal anesthesia appear significant. If essential hypertension is due to a circulating pressor substance similar to or identical with the one produced by renal ischemia, as has been postulated by many, and if this substance is not almost instantaneously destroyed or excreted, and if it produces its pressor effect by peripheral vasoconstrictor action, it is logical to conclude that it would continue to produce its pressor action as long as it is present in the body, unless something occurred to render the peripheral vascular mechanism incapable of reacting to vascoconstrictor substances. The marked elevation of blood pressure caused by epinephrine while the blood pressure was at its lowest level due to spinal anesthesia clearly indicates that the arterioles have not lost their capacity to react to peripherally acting pressor substances as a result of spinal anesthesia. We conclude, therefore, that the elevated blood pressure of essential hypertension is probably not due to a circulating pressor substance unless this substance is one which is destroyed or excreted almost instantly. If we admit the possibility that essential hypertension is due to a pressor substance that is destroyed very quickly, we must conclude that essential hypertension and hypertension due to renal ischemia are not caused by the same pressor substance. We doubt that essential hypertension is due to a humoral mechanism. We believe that data we have presented and literature we have analyzed support the probability that essential hypertension is due to vasomotor abnormality of central nervous system origin.

SUMMARY

The effect of spinal anesthesia on the blood pressures of ten individuals with normal blood pressures and twenty individuals with essential hypertension has been studied and the resulting data have been tabulated and graphically presented. The effect of epinephrine on blood pressures of hypertensive patients has been investigated by injecting this substance at the time the pressures were at their lowest as a result of the fall due to spinal anesthesia. The literature concerning the renal, vasomotor, and particularly the humoral etiology of hypertension has been reviewed. The literature relating to the duration of action of the humoral substance which causes hypertension of renal ischemia has been discussed as it may pertain to the cause of essential hypertension.

CONCLUSIONS

Spinal anesthesia has little and often no effect on the level of normal blood pressures.

Spinal anesthesia may produce a profound fall in the blood pressures of patients with essential hypertension.

This fall in pressure may occur in hypertensives with serious organic renal disease. This suggests that the fall is not due to improvement in the circulation through the kidney.

Six to twelve hours up to several days may be required for elevated blood pressures due to renal ischemia to fall to normal in both man and animals following correction of renal ischemia. A number of hours to days are required for renal ischemia to cause hypertension in animals.

Two to ten minutes are required for spinal anesthesia to cause a profound fall in the blood pressures of patients with essential hypertension. After the usual forty-five to sixty minutes of local anesthetic action has worn off, the blood pressures rapidly return to or approach the pre-experimental levels within a relatively few minutes. This rapidity of action suggests a strictly neurological basis for the mechanism by which spinal anesthesia causes a fall in the level of blood pressures of patients with hypertension. It suggests also the likelihood of an etiological relation of vasomotor impulses to the cause of essential hypertension.

Comparison of the long action of the humoral substance probably responsible for hypertension of renal ischemia with the rapidity with which the blood pressure of patients with essential hypertension fall as a result of spinal anesthesia makes it likely that essential hypertension and hypertension due to renal ischemia are due at least to different substances.

The functional integrity of the peripheral vasoconstrictor apparatus of patients with essential hypertension at the time when their blood pressures are at the lowest levels due to the spinal anesthesia is evidenced by the usual vasoconstrictor action of epinephrine. This suggests that essential hypertension may not be due to a circulating, peripherally acting pressor substance.

The data and analyses presented do not support the humoral etiology of essential hypertension but suggest a vasomotor etiology of central nervous system origin.

TABLE I. BLOOD PRESSURE IN MILLIMETERS OF MERCURY TAKEN AT INTERVALS OF TEN MINUTES BEFORE SPINAL ANESTHESIA ON A GROUP OF PATIENTS WITH NORMAL BLOOD PRESSURES

Name	Start		10 Min.		20 Min.		30 Min.		40 Min.		50 Min.		60 Min.		70 Min.		80 Min.		90 Min.		100 Min.		110 Min.		120 Min.		130 Min.		140 Min.		150 Min.	
	S	D	S	D	S	D	S	D	S	D	S	D	S	D	S	D	S	D	S	D	S	D	S	D	S	D	S	D	S	D	S	D
A. J.	108	54	110	55	107	53	108	50	109	42	105	55	106	51	105	50																
J. S.	109	80	110	80	111	80	111	80	109	80	110	81	109	80	110	80	107	79	110	80	112	79	108	80	109	79	110	78				
J. F.	112	84	126	82	122	86	126	77	119	78	126	85	123	82	116	82																
S. H.	138	90	137	90	136	89	136	87	136	88	130	90	128	91	128	91	126	88	125	84	126	88	132	93	132	94	133	94	134	92	134	96
J. H.	125	80	125	83	126	85	123	82	124	82	124	81	126	82	126	82	127	82	127	82	128	82	129	81	130	80						
D. R.	129	78	122	78	124	78	124	80	124	78	118	74	116	75	118	74	118	75	122	78	117	75	118	74	121	75	122	75	126	76		
J. M.	134	91	134	89	134	87	134	86	133	88	133	88	134	86	135	82	131	82	129	83	129	85	130	84	132	82						
L. S.	126	87	123	87	118	85	114	85	118	85	116	85	102	85	100	84	100	79	104	79	103	80	101	81	101	81	102	80	102	81	105	81
R. G.	152	92	144	93	134	94	125	93	123	90	123	87	124	85	125	83	126	81	129	91	129	81	129	81	126	81	127	81	127	82		
T. M.	118	80	109	79	105	76	108	78	110	83	112	87	116	90	118	90	118	88	116	82	112	78	106	78	110	76	106	78				
A. H.	110	78	113	81	110	80	112	79	112	80	112	81	110	79	111	80	113	81	112	80	110	80	111	82	112	81	113	79	111	80	111	82
O. H.	111	74	110	79	112	79	109	80	112	80	116	82	118	84	114	81	113	80	115	80	117	79	115	81	118	81	120	81				
Av.	124		122		120		119		119		119		118		117		118		119		118		118		119		117		120		117	
Av.		81		81		81		80		77		81		81		80		82		81		81		82		81		81		82		86

S—Systolic, D—Diastolic Blood Pressures in Millimeters of Mercury.

TABLE II. BLOOD PRESSURES IN MILLIMETERS OF MERCURY TAKEN AT INTERVALS OF TEN MINUTES DURING SPINAL ANESTHESIA ON A GROUP OF PATIENTS WITH NORMAL BLOOD PRESSURES

Name	Start		10 Min.		20 Min.		30 Min.		40 Min.		50 Min.		60 Min.		70 Min.		80 Min.		90 Min.		100 Min.		110 Min.		120 Min.		130 Min.		140 Min.		150 Min.		160 Min.		170 Min.	
	S	D	S	D	S	D	S	D	S	D	S	D	S	D	S	D	S	D	S	D	S	D	S	D	S	D	S	D	S	D	S	D	S	D	S	D
A. J.	103	67	103	66	102	66	100	65	97	65	103	64	100	68	101	64	102	67	102	67	104	66	104	67	106	68	106	68	100	69						
J. S.	110	69	118	75	127	74	126	72	119	70	116	68	113	68	119	72	123	72	122	72	125	72	122	72	115	76	113	72	116	71	116	72				
J. F.	118	69	100	52	91	51	100	60	110	72	100	76	106	75	110	72	110	72	111	74	114	71	111	74	114	74	114	76								
S. H.	134	83	138	85	136	88	132	80	123	79	111	79	117	76	119	73	122	74	120	78	119	77	120	78	116	78	114	74	119	78	118	78				
J. H.	119	78	120	82	124	76	119	76	116	75	114	79	114	84	120	86	121	84	121	84	119	82	121	84	124	75	119	74								
D. R.	125	74	129	76	120	59	120	74	117	71	104	69	114	79	124	84	117	80	119	83	118	77	119	83	114	78	111	72	115	75						
J. M.	130	80	132	81	133	80	128	79	126	78	130	78	134	76	133	78	132	78	131	78	131	78	131	78	132	80	133	82	132	82	132	80	133	78		
L. S.	126	80	122	79	120	63	123	67	114	67	112	66	112	65	111	64	114	66	113	72	112	80	113	72	109	64	106	65	107	68	111	70	116	73	119	73
R. G.	120	76	92	62	96	64	120	72	123	76	125	80	126	82	128	82	128	69	127	80	126	85	127	80	126	83	126	82	125	84						
T. M.	126	82	127	78	99	64	92	60	92	63	100	70	104	72	99	71	99	72	99	74	100	67	99	74	96	63	101	69	99	69						
A. H.	127	86	128	88	124	85	121	78	122	85	123	83	120	80	116	78	114	78	108	76	105	74	108	76	114	80	115	81	118	79	118	84	115	82		
O. H.	107	75	113	74	119	76	120	76	115	73	115	68	116	66	114	65	118	67	118	71	115	74	118	71	122	76										
Av.	120		119		116		117		115		113		115		116		117		116		116		116		116		114		115		119		121		119	
Av.		77		75		71		72		73		73		74		74		73		76		75		76		75		74		75		77		78		73

S—Systolic, D—Diastolic Blood Pressures in Millimeters of Mercury.

TABLE III. BLOOD PRESSURES IN MILLIMETERS OF MERCURY TAKEN AT INTERVALS OF TEN MINUTES BEFORE SPINAL ANESTHESIA ON A GROUP OF PATIENTS WITH HYPERTENSION

Name	Start		10 Min.		20 Min.		30 Min.		40 Min.		50 Min.		60 Min.		70 Min.		80 Min.		90 Min.		100 Min.		110 Min.		120 Min.		130 Min.		140 Min.	
	S	D	S	D	S	D	S	D	S	D	S	D	S	D	S	D	S	D	S	D	S	D	S	D	S	D	S	D	S	D
E. W.	230	130	230	128	228	124	228	124	230	122	236	122	232	126	230	130	226	134	228	130	228	122	228	126	228	128	228	130		
L. C.	198	122	196	126	186	124	196	126	196	130	188	126	182	122	178	124	176	130	176	120	200	130	236	138	264	150	240	142		
M. W.	176	126	178	128	182	128	184	130	188	132	186	132	186	132	186	130	188	132												
J. M.	232	128	228	126	228	126	228	124	230	120	236	120	220	124	220	132	238	130	230	132	226	134	230	134	228	138	232	130		
J. B.	180	112	178	110	174	104	168	94	166	94	170	94	184	110	185	110	186	108	195	118										
M. C.	210	120	210	120	210	120	210	120	210	120	210	210	210	120	210	120	210	120	210	120	210	120	210	120	210	120				
L. R.	160	80	160	90	160	90	160	100	160	90	160	90	160	80	160	80	160	90	160	90	160	80	160	80	170	90				
L. W.	204	94	240	110	244	124	230	116	240	116	228	114	240	122	242	122	238	110	238	108	236	110	238	114	236	120	258	124		
W. G.	200	110	196	106	196	100	200	100	202	100	204	98	204	100	204	100	200	100	200	100	204	110	204	110	202	114	202	110	206	110
V. D.	248	160	248	156	246	156	246	156	246	156	246	146	236	140	220	140	226	140	230	140	240	142	248	148						
L. G.	190	110	190	112	193	114	194	114	194	114	194	114	194	114	194	114	192	114												
L. J.	184	120	184	120	184	120	186	120	192	120	196	120	194	122	194	122	196	122												
O. B.	230	150	250	140	250	138	250	138	248	138	244	130	240	128	242	128														
J. S.	210	120	214	124	220	126	220	130	220	126	220	126	218	126	218	130														
J. A.	180	112	190	118	180	112	160	100	168	94	160	94	168	100	168	104	168	106												
A. K.	208	108	206	108	204	108	200	110	198	110	200	108	200	108	204	108	206	102												
A. J.	152	102	168	108	158	106	182	122	158	118	180	130	180	128	180	124														
M. Ca.	172	94	176	98	170	98	172	100	170	98	168	98	172	100	170	98														
Av.	198		202		201		201		201		200		201		203		201		207		213		219		220		232		206	
Av.		117		118		118		118		117		116		117		118		117		118		119		121		123		127		110

S—Systolic, D—Diastolic Blood Pressures in Millimeters of Mercury.

TABLE IV. BLOOD PRESSURES IN MILLIMETERS OF MERCURY TAKEN AT INTERVALS OF TEN MINUTES DURING SPINAL ANESTHESIA ON A GROUP OF PATIENTS WITH HYPERTENSION

Name	Start		10 Min.		20 Min.		30 Min.		40 Min.		50 Min.		60 Min.		70 Min.		80 Min.		90 Min.		100 Min.		110 Min.		120 Min.		130 Min.		140 Min.		150 Min.		160 Min.		170 Min.	
	S	D	S	D	S	D	S	D	S	D	S	D	S	D	S	D	S	D	S	D	S	D	S	D	S	D	S	D	S	D	S	D	S	D
E. W.	214	124	180	184	184	94	160	86	120	82	118	90	128	78	140	100	150	104	152	102	164	100	168	94	170	92	172	92	174	98	182	106	192	110	192	110
E. W.	224	122	190	100	80	58	84	50	100	60	104	62	218	90	264	102	230	96	250	94	284	84	210	94	210	96										
L. C.	242	144	200	112	168	106	134	90	152	90	164	104	158	100	170	104	184	105	190	112	190	120	196	118	180	112	162	100	198	118						
L. C.	238	148	184	120	154	114	154	112	164	116	150	100	140	104	160	108	180	120	206	120	218	140	220	148	226	144	220	132	226	140						
M. W.	162	114	142	106	120	84	120	82	124	92	132	100	140	100	132	94	142	102	164	116	162	116	168	114												
J. M.	258	148	236	126	162	88	92	66	80	68	84	53	86	54	154	60	174	82	164	72	178	80	198	100	200	104	200	104	200	104						
J. B.	190	120	182	98	140	84	136	84	134	80	122	72	122	80	106	68	98	68	110	66	120	70	150	80	156	98	160	90	162	90	160	92				
M. C.	216	136	198	130	172	110	162	110	174	112	180	112	172	114	170	110	170	110	172	110	168	100	170	102	164	100	170	100	170	104						
L. R.	170	90	150	72	120	70	116	68	106	64	118	70	104	68	104	68	110	70	116	68	112	68	128	80	128	80	126	72	130	76	122	78	128	76		
L. W.	240	116	142	80	108	70	122	80	130	80	144	80	164	80	168	86	184	92	194	96	198	106	198	116	200	120	206	122	210	120	212	120				
W. G.	186	90	148	80	122	66	118	70	100	62	90	62	104	66	100	70	104	66	116	72	120	74	130	80	132	72	144	82	148	90	150	90				
V. D.	250	144	220	132	152	114	144	106	112	92	130	92	160	100	162	102	198	120	208	122	228	120	224	128	220	128	232	132	230	130						
L. G.	178	102	164	100	164	96	148	84	140	84	140	84	152	88	152	88	150	92	119	80	150	82	162	92	190	96	190	98	170	100						
L. J.	178	128	176	122	170	120	172	128	184	126	178	116	178	116	184	118	180	118	186	122	182	124														
O. B.	244	124	126	124	126	92	140	92	142	102	152	104	164	106	188	110	202	120	202	130	240	140	246	140	250	138	250	138								
J. S.	220	126	210	122	194	118	164	100	164	94	170	96	168	84	166	88	166	78	146	78	150	80	162	88	170	90	172	94	182	102	200	106	200	106		
J. A.	164	106	160	108	168	100	150	92	148	92	138	86	136	84	140	86	150	98	160	84	170	86	180	82	200	86	190	90	190	90	180	88	170	90		
A. K.	192	108	192	108	196	100	112	60	112	64	112	68	114	72	122	68	122	78	130	76	148	82	148	84	162	92	172	96	168	96	170	96				
A. J.	168	102	164	104	158	108	154	110	158	110	152	110	156	110	152	110	156	110	160	110	170	120	172	114	168	112	162	120	170	126						
M. Ca.	152	102	140	82	130	72	122	78	138	78	134	82	128	82	132	88	132	88	130	86	140	82	132	90	142	100										
Av.	204		175		150		136		138		137		146		153		159		167		175		177		182		183		182		171		170		192	
Av.		120		110		93		89		88		89		90		92		96		96		99		102		103		104		105		96		95		110

S—Systolic, D—Diastolic Blood Pressure in Millimeters of Mercury.

TABLE V. THE EFFECT OF EPINEPHRINE ON THE BLOOD PRESSURES OF TEN PATIENTS WITH ESSENTIAL HYPERTENSION DURING THE PERIOD OF BLOOD PRESSURE FALL PRODUCED BY SPINAL ANESTHESIA

Patient	Blood Pressure Before Spinal Anesthesia Mm. Hg.	Blood Pressure After Fall Produced by Spinal Anesthesia Mm. Hg.	Epinephrine Chloride 1:1000 Solution		Blood Pressure Level Due to Epinephrine Mm. Hg.	Onset of Rise	Duration of Rise Min.	Subsequent Levels of Blood Pressure Millimeters of Mercury
			Amount	Route				
E. W.*	220/122	80/54	0.5. cc.	H.	110/84	Slow	5	
E. W.*	220/122	110/62	1.0 cc.	I. M.	235/106	Immediate	11	Fell to 218/90 then rose to 265/106
J. M.*	258/150	80/56	0.3 cc.	H.	110/70	Slow over a period of 5 min.	10	Fell to 88/52 gradually rose
J. A.	170/108	130/84	1.0 cc.	I. M.	210/110	Immediate	10	Fell to 170/82
L. G.	186/118	140/84	0.8 cc.	H.	154/88	Very slowly 15 min.	10 – 12	
R. S.	140/98	56/42	0.6 cc.	H.	80/60	Slow over 5:10 min.	12 – 15	
W. E.	180/130	126/104	0.3 cc.	I. V.	280/220	Immediate	12	Fell to 126/114
M. T.	240/154	160/130	0.2 cc.	I. V.	280/160	Immediate	10	Fell to 182/120 gradually rose to 270/130
J. M.*	205/125	150/100	1.0 cc.	H.	190/110	Slowly 10-15 min.	?	
L. M.	210/134	160/104	0.1 cc.	I. V.	320/160	Immediate	8-10	Fell to 150/105

* Refers to same patient.
H—Hypodermically, I. M.—Intramuscularly, I. V.—Intravenously.

* Refers to same patient.
H—Hypodermically, I. M.—Intramuscularly, I. V.—Intravenously.

TABLE VI.

EFFECT OF VOMITING ON BLOOD PRESSURE

Patient	Blood Pressure Before Spinal Anesthesia Mm Hg.	Blood Pressure After Fall Produced by Spinal Anesthesia Mm. Hg.	Blood Pressure Level due to Vomiting	Onset of Rise	Duration of Rise Minutes	Subsequent Levels of Blood Pressure in Millimeters of Mercury
V. D.*	248/142	112/94	190/120	Immediate	10	Fell to 128/92
V. D.*	248/142	128/92	192/130	Immediate	5	Fell to 152/96
M. T.	244/154	152/110	204/166	Immediate	10	Fell to 154/130
A. K.	192/110	112/60	160/98	Immediate	15	Fell to 114/68

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CALLING ATTENTION TO: ITEMS OF POSSIBLE INTEREST TO FRIENDS OF OUR EFFORT

MAY, 1943

1. **Abstracts:** Probably are best way to get out ideas these hectic days! Those of the Detroit **American Chemical Society** April meeting may be obtained from ACS 1155 16th St. NW, Washington, D. C. W. P. terHorst notes high fungicidal action of dichloronaphthoquinone. G. J. Martin shows that sulfonamides increase nutritional requirements. F. H. Schultz & Co. of Stamford confirm our self-aid ideas in handling war gas exposure. Lots on anti-malarials: K. C. Frisch & M. T. Bogart find veratrole derivatives interesting; M. T. Leffler studies 9-aminoalkyl-aminoacridines. F. Bernheim & Co. find iodine aromatics inhibit tubercle bacilli (triiodo-benzoic acid is non-toxic for humans). F. Linsker & M. T. Bogert study amidino arsenicals, which should be broad chemotherapeutic agents. D. L. Tabern finds desoxyephedrine a volatile vasopressor. **Federation Proceedings Abstracts** (2: 1-106, 1943) also reflect interest in antimalarials: A. C. Ivy & Co. find moderate retention of atabrine, with considerable excretion in bile and urine; R. E. Hewitt & A. P. Richardson show that effective antimalarials cause degenerative changes in plasmodia; F. J. Stare & Co. note little nutritional interference from atabrine, except in high doses (40 mg/kg). J. F. McClendon claims prevention of dental caries by brushing with fluorapatite. M. B. Chenoweth & W. Modell partially extract active uterus relaxing principle from raspberry leaves. And, of course, there are many notes on effects of low oxygen tension. Also the Physiological Society reports almost as many pharmacological papers as the Pharmacology Society.

2. **The Great James Blake Lab Gang:** B. Abreau finds that morphine reduces uterine action while demerol does not (**Fed. Proc.**, 2:73, 43). G. Alles turns out a pair of honeys on amine oxidase (**J. Biol. Chem.**, 147: 487, 505, 1943). L. Chan, S. Spiradanoff & E. Way observe biological interference between thiopantothenic acid & pantothenic acid (**Fed. Proc.**, 2: 92, '43). G. A. Emerson, J. Finnegan & J. Morrison report bacteriostatic & choleretic effect of chloroacetate (**Ibid.**, p. 78). E. R. Hart notes antagonistic action of N-allyl-normorphine against morphine (**Ibid.**, p. 82) P. K. Knoefel finds phenisopropyl amines (benzedrine & Pervitin) increase work output (**Ibid.**, p. 83). S. A. Peoples shows that ether completely inhibits hypoglycemic action of insulin, as predicted erstwhile (**Ibid.**, p. 88). D. Marsh notes neoarsphenamine causes rise in pulmonary blood pressure (**Ibid.** p. 87). Some gang! F. P. Luduena even gives it a boost (**Rev. Med. Rosario**, 33: 84, 1943). Here's to James Blake!

3. **Still More Books: Protein Hormones of the Pituitary Body** by H. Van Dyke, B. Chow, H. Fevold, G. Irving, C. Long, V. du Vigneaud, is issued by the Annals of the New York Academy of Science (63: 6, 1943). Commonwealth Fund publishes revised ed. I. F. Huddleson's **Brucellosis in Man & Animals**, & G. L. Muller's **Clinical Significance of Blood in Tuberculosis.** Cattell Press, Lancaster, offers E. F. Adolph's

Physiological Regulation, dealing with water balance ($7.50). A. W. Franks of Montreal has 4 vols. of T. Selve's **Index of Steroid Hormones** for $19.50; Internat. Labor Office issues **Occupation & Health** in 2 vols. at $20.00 (World Peace Foundation, 8 W. 40th St. NYC). And F. H. Albee tells about his **Surgeon's Fight to Rebuild Men.**

4. **Tooting Our Own:** D. Calvin says maternal parathyroid deficiency increases fetal thymus (**Fed. Proc.**, 2: 5, '43). W. Collings, H. Swann, C. Dernehl & J. Cline note more insensible water loss on exposure to low pressure (**Ibid.**, p. 7). E. Porter & E. Callahan find ischemia improves neuromuscular conduction, may cause overcontraction, as in intermittant claudication, (**Ibid.**, p. 38). W. Selle studies periodic discharges of respiratory center (**Ibid.**, p. 44). F. Schlenk inactivates codehydrogenase I by alkali (**Ibid.**, p. 70). P. Ewing & F. Schlenk find adeninethiomethyl pentose has less untoward effects than adenosine when used in treating nutritional deficiencies (**Ibid.**, p. 78). R. Gregory, P. Ewing & H. Levine suggest azotemia from gastric bleeding may be due to absorption of digested blood (**Ibid.**, p. 81). E. Porter & J. Lockhart indicate that there may be real antagonism between morphine & strychnine (**Ibid.**, p. 89). E. Poth & C. Ross find phthalylsulfathiazole superior to the succinyl derivative in controlling watery diarrhea (**Ibid.**, p. 89). J. Roberts et al. report on nourishment of the heart (**Ibid.**, p. 90). Some gang, too!

JUNE, 1943

1. **Reviews:** Really hot, says M. Shimkin, is J. P. Greenstein's survey of tumor enzymology (**J. Nat. Cancer Inst.**, 3: 419, 1943). Then there's N. J. Berrill's study of malignancy in relation to organization & differentiation, & A. Dorfman's reviews of pathways of glycolysis (**Physiol. Rev.**, 23: 101, 124, 1943). Also note C. Monge's survey of chronic mountain sickness (**Ibid.**, p. 166). W. Rabb reviews the pathogenic significance of adrenalin & its relatives for heart muscle (**Exp. Med. & Surg.**, 1: 188, 1943). H. C. Clark goes over recent work on prophylaxis & treatment of malaria (**J. Nat. Malaria Soc.**, 1: 113, 1943). J. N. Davidson offers brief summary with big bibliography of "wound hormones" (**Edin. Med. J.**, 50: 70, 1943). A. Lipschitz summarizes his studies on endocrine aspects of antitumoral autodefense (**Rev. Canad. Biol.**, 2: 92, 1943). L. Brouha & Co. survey work on "step test" measure physical fitness for hard muscular labor (**Ibid.**, p. 86). L. W. Shaffer reports on present status of intensive arsenotherapy of early syphilis (**Ven. Dis. Info.**, 24: 108, 1943). E. W. Thomas & G. Wexler do likewise (**Arch. Dermat. Syph.**, 47, 553, 1943).

2. **Symposia:** Pleasant one on impetigo (**Lancet**, 244: 544, 547, May 1, 1943). Important one on scientific proof & relations of law & medicine (**Ann. Int. Med.**, 18: 445-697, 1943). Interesting one on stuttering in remarkable new journal **The Nervous Child** (2: 79, 1943).

3. **Shock:** In elaborate studies on traumatic shock, J. Fine, A. Seligman & Co. find that oxygen has no value in hemorrhagic shock (**J. Clin. Invest.**, 22: 265-305, 1943). F. L. Engel, M. G. Winton & C. N. Long show that hemorrhagic shock causes liver & tissue injury from anoxia with increased proteolysis & lactate & pyruvate accumulation (**J. Exp. Med.**, 77: 397, 1943). G. F. Kamen (**Proc. Soc. Exp. Biol. Med.**,

52: 363, 1943) suggests that lipoid breakdown products like acrolein may have some causative relation to shock. J. P. Levinson & H. E. Essex (Ibid., p. 361) show that peripheral vasoconstriction occuring in shock is not dependent on an intact nerve supply. P. L. Mollison discusses hemolytic transfusion reactions (Brit. Med. J., 2: 529, May 1 & 8, 1943).

4. **A Few Books:** C. C. Thomas (Springfield, Ill.) publishes C. L. Gemmill's **Physiology in Aviation,** an inexpensive and brief item. J. B. Sumner & G. F. Somers issue **Chemistry & Methods of Enzymes** (Academic Press, N. Y.). G. L. Walls writes on **The Vertebrate Eye & Its Adaptive Relations** (Cranbrook Inst. Science, Bloomfield Hills, Mich.). J. H. Masserman discusses **Behavior and Neurosis** (Univ. Chicago). Oxford issues E. J. Bowen's **Chemical Aspects of Light.** C. C. Thomas (Springfield, Ill.) also publishes J. A. Reyniers **Micrurgical & Germ-Free Methods: Their Application to Experimental Biology and Medicine.** And here's another salute to Herbert Evans—for whose 60th birthday the University of California publishes a special volume of scientific tributes. Stanford Press will issue A. C. Reed's **Tropical Medicine.**

5. **Alia:** H. A. McGuigan's ideas on mass hysteria hide a pertinent point (J. Asso. Am. Med. Col., 18, 182, 1943). Why have scientific periodicals—**read Life!** And did you note the article about our L. L. Lumsden in Satevepost? Of course, development of resistance to penicillin is noted (L. H. Schmidt & C. L. Sesler, Proc. Soc. Exp. Biol. Med., 52: 353, 1943.) M. R. Sapirstein finds glutamic acid controls ammonium ion enzymatically in brain & thus may control epileptic convulsions (Ibid., p. 334). C. Gutierrez-Noriega notes metrazol convulsions due to summation of local stimuli augmenting direct action of the drug on motor neurones: there is no evidence for a convulsant center (J. Neuropath. Exp. Neurol., 2: 132, 1943). J. J. Pfiffner & Co., isolate antianemic factor from liver in crystalline form (Science, 97: 404, 1943). B. C. McIvor & S. P. Lucia describe method of getting anti-Rh serum (Proc. Soc. Exp. Biol. Med., 52:-293, 1943).

JULY, 1943

1. **Once Again, Here's to You, Herbert:** Univ. California Press at $10.00 offers a choice collection of 48 papers on physiology of reproduction, nutrition & endocrines, and on the history of medicine & science, **Essays in Biology in Honor of Herbert M. Evans.** From Allen, through Fulton, Houssay & Turpeinen, to Zondek, the essayists have given Herbert a grand 60th birthday. Don't miss a one; they're all first class. The volume is a must for any library.

2. **Other Books:** H. F. Blum offers **Photodynamic Action & Diseases Caused by Light,** an excellent survey (Reinhold Publ. Co., New York City, $6.00). F. J. Wampler edits for Williams & Wilkins, Baltimore, $6.00, the **Principles & Practice of Industrial Medicine,** with chapters by 32 experts. Basic & hot is H. A. Abramson, L. S. Moyer & M. H. Gorin's **Electrophoresis of Proteins and the Chemistry of Cell Surfaces,** (Reinhold Publ. Co., New York City). Tops is **Proteins, Amino Acids & Peptides as Ions & Dipolar Ions** by E. J. Conn & J. T.

Edsall (Reinhold Publ. Co., N.Y.C.). The Commonwealth Fund (41 E 57th St., New York 22) issues D. O'Hara's **Air-Borne Infection: Some Observations on its Decline.** On the sweetness and light side is B. W. Overstreet's **Courage for Crisis** (Harper's, N.Y.). J. B. Lippincott, Philadelphia, refer to L. K. Ferguson's **Surgery of the Ambulatory Patient** as the Book of the Year. From the MacMillan Co., Cambridge Univ. Press Division, N.Y.C. comes the announcement of the intriguing **Anonymous Londinensis,** a translation by W. H. S. Jones of 2nd Century papyrus giving extracts from 25 ancient medicos. Also for $5.50 the important **Permeability of Natural Membranes** by H. Davson & J. F. Danielli. And C. E. Raven's **Science, Religion & the Future.** Noticed the increase in manuals of tropical medicine and parasitology? Annual Reviews (Vol XII, Biochemistry; Vol. 5, Physiology, Stanford Univ., Calif.) are up to their usual standards. For the American Library Association, Chicago, Janet Doe of the New York Academy edits a **Handbook of Medical Library Practice,** which let's hope won't become pontifical.

3. **Shock:** F. R. Winton & Co. describe injury to kidneys from traumatic shock (**Quart. Jour. Exp. Physiol.,** 32: 89, 1943). M. C. Winternitz & Co., show significant rise of serum phosphate in traumatic shock & demonstrate shock like symptoms from phosphate administration, and then indicate beneficial effect of intravenous sodium succinate (instead of glucose) with plasma (**Am. Jour. Physiol.,** 139: 299-324, 1943).

4. **Cancer:** J. K. Parnas succinctly reviews coenzymatic reactions (**Nature,** 151: 577, May 22, 1943).The excellent work of the McArdle Lab at Wisconsin results in W. C. Schneider & V. P. Potter proposing theories of biocatalysis in cancer tissue (**Cancer Res.,** 3: 353, 1943). I. H. Perry, L. A. Strait & E. L. McCawley put across a neat California report on a spectrochemical study of estrogen-induced mammary cancer (**Ibid.,** p. 370-384). C. Huggins discusses the endocrine control of prostatic cancer (**Science,** 97: 541, June 18, 1943).

5. **Alia:** W. Hughes & F. Murgatroyd discuss drug control of malaria (**Lancet** 244: 699, June 5, 1943). Vale to Warrington Yorke (1883-1943), brilliant chemotherapist! M. M. Sheniakin & Co. (Moscow) (**Nature,** 151: 585, May 22, 1943) also propose a redox mechanism for vitamin K activity, like E. L. McCawley & C. Gurchot (**Univ. Calif. Pub. Pharmacol.,** 1: 325, 1940). E. C. Dodds & Co. naturally would note morphine-like action of diphenylethylamines (**Nature,** 151: 614, May 29, 1943). W. S. McClellan of Saratoga Springs would also naturally observe new trends in the treatment of chronic disease, recounting an experience in Spa therapy (**Ann. Int. Med.,** 18: 825, 1943). E. A. Doisy & Co. report that penicillin B is a flavoprotein enzyme causing oxidation of glucose to gluconic acid & hydrogen peroxide, the latter being antibacterial (**J. Biol. Chem.,** 148: 365, 1943). The J. R. Gallaghers & L. Brouha give dope on dynamic physical fitness in adolescents (**Yale J. Biol. Med.,** 15: 657, 1943). G. A. Emerson finds that venticular fibrillation from digitalis is not adrenergic (**Proc. Soc. Biol. Med.,** 53: 12, 1943).

A NEW ERA IN MILITARY SURGERY

I. S. RAVDIN*

Ambroise Pare, the great barber-surgeon of France, who might well be called the Father of Surgery, in a moment of rare wisdom wrote "The Chirurgeon . . . will . . . seek all means for the quick recovery of the Patient; lest that which of its own nature is small, may by his negligence become great." Recently William Darrach in a paper entitled "The Care of the Lightly Wounded" said, "Most of these patients . . . should have been able to return to duty within a few few weeks. . . . I feel very strongly that the care of the lightly wounded as I saw it in France was greatly neglected." The importance of adequate medical care for the military forces of this country has long been recognized, for early in our War for Independence, John Morgan, who founded the Medical School of the University of Pennsylvania, became the Director General and Physician-in-Chief of the American Hospital. During the first World War 7,000,000 men lost their lives, most of these as the result of injuries received during warfare. No one knows, or would attempt to predict the number of casualties that will take place in the present global conflict, but it is quite probable that the number of dead will greatly exceed that of 1914-1918, and possible that it may have already passed it, for this war is on a wider scale and the weapons of warfare are more terrible than ever before.

We are however, much better prepared to treat our lightly and seriously injured than we were even a quarter of a century ago. The advances in medical science have been such as to raise high hopes that many of our injured men, who twenty-five years ago would have died, can now be saved; that many who previously would have been permanently maimed can now be restored to normal health; and that prolonged convalesence in many instances can be done away with. It is some of these advances in therapy that I should like to discuss with you today. Time will not permit me to review all of them, but I shall se-

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lect a few which will without doubt play an important role in the care of battle casualties.

The Prevention and Control of Infection in Wounds and the Care of Fractures: General Love in a report on casualties of the U. S. Army during the last war stated that 54 per cent were wounds of the soft parts of the extremities, while 29 per cent were compound fractures of the extremities. Available accurate bacteriologic data from the first World War are limited, but those that can be relied upon are illuminating. Stokes and his colleagues reported that about 15 per cent of patients with wounds were already infected with hemolytic streptococci when admitted to Base Hospitals. Leonard Colebrook believes that the hemolytic streptococcus was responsible for 70 per cent of all deaths due to wounds. I am sure that reports, which will later be available to us, will show that these organisms have been the cause of much unnecessary suffering, prolonged convalesence with deformity, and death, in innumerable instances during the early phases of the present conflict.

The work of many unbiased investigators of the past decade points strongly to the fact that skin antisepsis is unattainable and that most of the substances now being used in an attempt to provide this are no better than a simple soap and water scrub and the subsequent application of alcohol, or acetone, or both. What has been shown for supposed skin antisepsis, applies even more to wound antisepsis. Many of the agents previously used, too many of which continue to be depended upon in civilian practice, are protoplasmic poisons. They may adversely influence bacterial growth, but they nearly all also retard wound healing.

It has been shown by Smith, Carnetsky and Mudd that many of the antiseptic agents, particularly the mercurials become completely ineffective as bacteriostatic or bactericidal agents, when in contact with very small amounts of serum protein. The heavy metals have a profound influence on enzymatic actions, and the frequent failure of wounds to heal, or the delay in healing during the daily exposure of regenerating tissues to large amounts of these

substances is without doubt due to the overzealous use of antiseptics containing such agents.

We now know that only active infection, the presence of devitalized, or necrotic tissue, or abnormalities in the biological factors which influence wound healing will prevent regeneration from taking place according to the Carrel-DuNouy formula. The single wound agent, widely used during the last World War, which continues to demonstrate its usefulness is Dakin's Solution and I agree with Anderson that this is very likely due to its ability to cause the solution of necrotic tissue, thus providing the conditions best suited for wound healing.

While these generalizations are true for a wide variety of the commonly used antiseptics there has become available within the last few years a group of compounds, the sulfonamides, which while they are possessed of great bacteriostatic effect when placed in a wound, or given orally, have little if any untoward effect on the tissues with which they come in contact. Their use in the prophylaxis and treatment of established infection has revolutionized the care of civilian injuries and is without doubt having a similar influence on the wounded in our armed forces. The widespread local and oral use of sulfanilamide and sulfathiazole in the casualties that followed the raid on Pearl Harbor just a year ago, led to results which were previously unheard of in military hospitals. It is true that the injured men were wearing clean clothes, were not soiled from days in trenches, and were as a rule treated relatively soon following injury, but it was also true that many of the wounds were badly contaminated with highly fertilized soil and that in many instances more than 24 hours elapsed before surgical treatment could be afforded the injured men.

The observations of Jensen, Johnsrud and Nelson, on the effectiveness of locally applied sulfanilamide in compound fractures occurring in civil life has now been verified in many theaters of operation. Previous to the use of locally implanted sulfanilamide the incidence of infection in their patients was approximately 27 per cent. Subsequent to the use of locally implanted sulfanilamide, other methods of treatment remaining the same, the incidence

of infection was but 4.4 per cent from all causes, or 3.3 per cent of primary infections. Of the many, many, extensive wounds and compound fractures which Perrin Long and I saw at Honolulu which were treated by debridement, irrigation, and the local implantation of a sulfonamide not a single virulent infection resulted and in innumerable instances the wound healing, and at times the bony union, was completed in less than three months. When we later saw many of these patients in hospitals along the West Coast, they were convalescing at an unprecedented rate, and there was not a single instance of widespread infection. While we cannot expect such universally favorable results in all of our casualties we can confidently look forward to the continued usefulness of sulfanilamide, sulfathiazole and sulfadiazine in the prevention of infection in contaminated wounds and the control of infection once established.

The experiments of Lockwood, Woods, McLeod and others, provide a more specific explanation of the mechanism of the action of the sulfonamides. They have demonstrated that these compounds act in the main by disrupting some nutritive mechanism which is essential to bacterial growth. Badly injured and necrotic tissues liberate an abundance of nutritive substances upon which bacteria can multiply. At the same time these nutritive substances definitely inhibit sulfonamide action. Their work explains why non-necrotizing lesions such as erysipelas and diffuse streptococcic cellulitis are controlled swiftly by sulfonamide therapy while infections characterized by extensive tissue necrosis and early suppuration, respond more slowly to these compounds. We now have a rational basis for adequate, careful wound debridement and thorough wound irrigation, for the sulfonamides will prove much more effective against bacteria, if the seriously injured tissue is excised and the products of tissue breakdown have been removed by irrigation.

Practices such as debridement and thorough wound irrigation which were found to be effective during the last World war when instituted in the first six hours following injury are thus by no means displaced by sulfonamide therapy. On the contrary they are given a new meaning. If crystalline sulfanilamide is placed in every wound with-

in a short time following injury, and the part immobilized as was done at Pearl Harbor, we can expect that the six hour period, previously believed to be the critical one for debridement, can be extended to twenty-four or even more hours, with confidence that a major infection can in most instances be prevented.

The effectiveness of zinc peroxide in controlling the development and spread of infections due to certain anaerobic organisms is another example of the developments in chemical bacteriostasis which will have a profound influence on injuries which occur in military engagements. If wounds are carefully debrided and irrigated, if sulfanilamide is locally applied to the wound and later left open, the incidence of anaerobic infections will be low, although they will not be eliminated. When they occur zinc peroxide or similarly acting substances will provide an environment that is not well suited for anaerobic bacterial growth and toxin production. It can be anticipated that these new chemical agents will aid greatly in reducing the incidence of amputations. Urea peroxide seems to warrant special study, for it may aid in dissolving and removing necrotic tissue.

Thus in the new substances such as the sulfonamides, azochloramide and zinc peroxide we have available materials which are not protoplasmic poisons destroying bacteria and tissue cells alike, but each in its special way so influencing the culture media as make it unfavorable for bacterial growth and invasion.

The new agents merely act as adjuvants to the older methods of treatment. They cannot replace the time tested adequacy of debridement, thorough wound irrigation and immobilization especially in the case of compound fractures and extensive soft part injury. Too many of our military casualties cannot receive adequate surgical care within six hours of the time of injury, for the exigencies of war prevent this. The initial introduction of adequate amounts of a bacteriostatic substance such as sulfanilamide will permit this critical period to be greatly extended and their use following operation will without doubt greatly reduce the incidence of primary and secondary infection.

The extension of the circular plaster method of treatment of certain compound fractures to include also the

extensive wounds will greatly reduce the incidence of secondary infection, for the increase in hemolytic streptococcus infection from 15 per cent in Casualty Clearing Stations to 90 per cent upon arrival at Base Hospitals as was found in certain theatres of operation in the last war, was, in part at least, due to contamination by dressers enroute.

In all modern wars the fractures have formed the greatest single number of casualties and of these the compound fractures are the most important. Early in World War I the British reported that the mortality from compound fractures of the femur was 50 per cent. They reduced this to 15 per cent by the application of Thomas splints by stretcher bearers. The three great problems which so frequently frustrate surgical care, delay, shock and infection, were the major factors in the residual mortality. Under the conditions of warfare there are often long periods of delay in the initial treatment, and in addition, multiple interruptions before final treatment can be established in a fixed hospital.

The early local implantation of sulfanilamide at the wound site and the use of aeroplane transports for the evacuation of seriously wounded to fixed hospitals will facilitate early definite treatment. The continued use of Thomas splints for first-aid immobilization and the early institution of permanent extension, if this is necessary, by one of the modern means of wire or pin extension with fixation with vitallium will permit of evacuation under conditions not previously attainable. Many of the fractures can be treated by the modified Orr-Trueta method without extension. Thus reduction and fixation will be attained with one procedure and secondary reductions will be reduced to a minimum. The modern mechanical devices for fixation, which many surgeons in civilian practice have called "gadgets" will have an extraordinary influence on the care of these casualties.

Shock can be controlled, or even prevented by the use of plasma or serum or albumin. Infection can in large part be prevented by careful debridement, thorough wound irrigation and the use of locally implanted sulfanilamide. Tetanus will be practically eradicated by our program of toxoid immunization. And reduction and fixation will be

improved by the adoption of the modern methods of fracture care such as the circular plaster splints for fractures not requiring continued extension, by pin or wire traction the pins or wire being incorporated into the plaster, or, if deemed advisable into some form of external appliance, or by internal fixation. Anaerobic infections will be reduced if surgeons will realize that in the extensive wounds no attempt should be made at wound closure, a lesson which some of our colleagues have not yet learned. No one who has seen these methods used as I did at Honolulu a year ago will doubt but that when the history of this war is written this section of it will form a brilliant chapter in surgical achievement.

The Control of Peritonitis following Abdominal injury:

In 1936 we began the use of parenteral sulfanilamide therapy to control spreading infections of the peritoneum from acute supporative appendicitis, and in 1938 began using the drug by local implantation in the peritoneum at the time of operation and by parenteral therapy if continued use seemed indicated, the former method having been adopted by Thompson and his associates at the Roosevelt hospital in New York. The continued use of this method of treatment has fully confirmed our earlier opinion that sulfonamide therapy would prove of great usefulness. For a concentration is attained which in view of the natural cellular defense of the peritoneum, is quite adequate, to inhibit the growth of organisms and to permit phagocytosis to proceed along very active lines. Under such circumstances the tide is frequently turned and what appeared to be a hopeless case, has, following operation and drug therapy, resulted in recovery. While sulfonamide therapy in such instances does not take the place of early and skillful surgical treatment it supplements it.

The extension of this method of therapy to prevent the spreading infection so frequently seen after bowel resections first suggested by Garlock and Seeley has given very satisfactory results. The use of similar methods in the perforations of the bowel following the raid on Pearl Harbor a year ago, was associated with the most gratifying results. Recently Loria of New Orleans has reported on the effectiveness of locally implanted sulfathiazole in

the control of spreading infection following gun-shot wounds of the bowel in civil life. The very substantial reduction in mortality which this complement to therapy afforded is an additional assurance that such drugs do affect intestinal pathogens and so serve to augment the natural defenses of the peritoneum to the extent that the balance of factors will become favorable to the host. We can, I believe, be confident that the sulfonamides will provide a substantial reduction in the morbidity and mortality with which such injuries were previously associated, for during the first World War the mortality of these injuries was approximately 86 per cent, while in Guadalcanal they have been approximately 5.0 per cent. The experience which we had at Honolulu has thus been repeated in other theaters of operation.

Wound Healing:

If infection can be prevented, or controlled, convalescence can be shortened by paying attention to certain biological factors which influence tissue regeneration. It was demonstrated during the last World War that patients with extensive suppuration such as a thoracic empyema could not be maintained in a state of positive nitrogen balance. It was furthermore demonstrated that when such patients were kept on a high caloric diet recovery was facilitated. The investigations of Walbach and Howe, Lanman and Ingalls, Crandon and Lund, Taffel and Harvey, Hartzell and Winfield, and Thompson, Ravdin and Frank, have demonstrated the importance of factors other than technical perfection which facilitate the rapid repair of injured tissues, and Goldschmidt, Ravdin and Vars, and Whipple and his associates have provided data on the protection which is afforded certain viscera from toxic agents by an effective diet.

We have become much more conscious of the part which proper nutrition plays in facilitating repair from injury. A vitamin "C" deficiency may lead to a failure in the laying down of collogen in healing wounds, and protein deficiency is too often associated with failure of wounds to undergo normal fibroplasia. It is now generally accepted that the loss of weight of patients in our hospitals is too frequently an expression of the extent to which we

are failing to meet the energy requirements of the individual. We have no statistics from military channels on the relationship of weight loss as an indicator of surgical risk but Studley in a most interesting sudy of the percentage of weight loss as a basic indicator of surgical risk in patients with chronic peptic ulcer found that when the weight loss "reached as high as 20 per cent or above, it was associated with a post-operative mortality of 33.3 per cent in contrast to a rate of 3.5 per cent among those who had lost less weight."

The Surgeon-General's office has an efficient group of men who are concerning themselves with the problems of nutrition in our armed forces. Even though we are feeding the civilians in this country and in many other lands, we are efficiently feeding our armed forces and supplementing the foodstuffs necessary for our allies. Every effort is being made to provide a diet adequate in total calories, in the necessary amounts of Vitamin C and other vitamins, and in protein for the armed forces. The Office of the Surgeon-General of the Army and the Bureau of Medicine and Surgery of the Navy, have circularized all medical officers calling attention to these important biological factors which influence tissue repair and protection, and they have stressed the importance of a well-balanced high caloric diet. We can confidently look forward to the more rapid repair of wounds in which invasive infection has been controlled or prevented and every possible aid provided to facilitate cellular repair.

Shock and the Blood Substitutes:

The brilliant researches of Underhill and his associates, of Blalock, and Parsons and Phemister and many others have demonstrated without doubt that the loss of an efficient and effective blood volume is the major factor in the development of shock following extensive injury of tissues, whether this be due to burns, to extensive contusion and laceration or hemorrhage. While it is highly possible that, under certain circumstances, a toxin produced at the site of injury further intensifies the condition, the factor that early initiates the shock process is a disparity between the amount of circulating blood and the size of the vascular bed. There remains some disagreement on just where

the loss of fluid occurs, whether it is in the main confined to the site of injury or whether there is a loss of fluid throughout the body as a consequence of general capillary injury. It would seem highly likely that, as a rule, the initial primary loss of plasma occurs at the site of injury, while the extensive generalized loss of fluid from the blood vessels takes place later when the disparity between blood volume and the size of the vascular bed is so great as to lead to marked slowing of the blood stream, to a deficient oxygen carrier and to consequent anoxia. Whether the absorption of toxins plays a part in this latter process is yet to be proven.

In these instances in which the reduction in blood volume is associated with a loss chiefly of plasma and little or no loss of red cells, there occurs a marked increase in the viscosity of the blood as the number of erythrocytes per cubic millimeter of blood increases. The addition of more blood by transfusion to the vascular system provides an additional number of red cells which will remain behind when the plasma in which they are suspended leaves the blood vessels. An additional load is thus placed upon the heart and gradually the already impaired circulation is further impeded and the shock process is accentuated.

While "bank blood" greatly increased the ease with which transfusions could be carried out, storage was not possible for long periods of time and under a variety of environmental circumstances. It was a result of the realization of these facts that numerous workers became interested in providing certain blood substitutes which do not contain the formed elements of blood.

First wet plasma and serum became available. The pooling of large amounts of these substances, from many donors, reduced the incidence of reactions following their use. It was found that serum which stood for some days before use was less likely to cause reactions than was freshly prepared serum. Strumia showed that these substances could be frozen and stored for long periods of time without change. These agents have greatly facilitated the care of the patient who is losing or has already lost, a considerable amount of his blood volume, a circumstance which may occur with extraordinary rapidity.

Rhoads, Wolff, Lee and Saltonstall have shown that in a burn of moderate severity involving only one lower extremity, the loss of as much as 1400 cc. of plasma may occur in from six to twelve hours, and that in burns involving only 15 to 20 per cent of the body surface 40 percent of the plasma volume may be similarly lost. In fact all of the results of recent investigations point to the importance of recognizing that the loss of plasma volume takes place early. If one of the first things to do following an extensive burn or serious injury is to prevent shock, and I am sure it is, then large amounts of the blood substitutes must be immediately available. While such materials in the wet state are quite satisfactory in this country, it is necessary that our armed forces throughout the world be provided with adequate amounts of readily transportable blood substitutes. During shipment they should require a minimum of space and they must be able to withstand temperatures that may vary from those encountered in the Arctic to those found along the Equator. The work of Flosdorff, Mudd and Reichel led to the methods which now provide for the drying of plasma and serum. The process of lyophilization, which they devised, has had numerous modifications, but the end result is essentially the same, a dried product which can be regenerated for use by the simple addition of sterile non-pyrogenic, water. The dried product can, and has been shipped throughout the world, it does not become altered by age, and it can withstand wide variations in temperature.

However, even with the greatest of care, a variable number of reactions occur following the use of these substances, and in many theaters of operation non-pyrogenic water is not always obtainable. When it is not such carefully prepared water must be shipped with the dried product.

These and other facts led Dr. Walter Cannon to suggest to Dr. Edwin Cohn of the Department of Physical Chemistry of Harvard Medical School to attempt to prepare pure crystalline human albumen. One of the most important researches which has received governmental support during the period prior to our entry in the war was that which led Dr. Cohn to the isolation of human albumin from plasma.

Since the albumin in plasma or serum is responsible for approximately 85 per cent of the colloid osmotic properties of these substances, it is the material most necessary, when as the result of increased capillary permeability, or hypoproteinemia, fluids are leaving the blood vessels at an abnormal rate. Albumin tends to remain in the blood vessels even in the presence of increased capillary permeability and to draw additional fluid from tissue spaces into them. In the absence of acute hemorrhage leading to a serious deficiency in the red blood cells it will answer every requirement of an immediate blood substitute. It can be transported in concentrated solution, 25 per cent, to the four corners of the earth, so that a small 100 cc. bottle contains the equivalent of one pint of plasma or one quart of blood. It will withstand the widest variations in temperature for long periods without deterioration. Since the globulin fraction of the blood has been removed reactions are practically unheard of. Here then is a contribution to the war effort which will assist greatly in making possible a new era in pre- and postoperative care. The possible preparation and use of albumin from species other than man would further open the way for the use of blood substitutes before shock has become manifested. Then truly will we be treating the serious casualties of warfare along the most enlightened physiological lines, for even corpsmen will be able to administer this life maintaining fluid to our casualties as they lie on the battlefield. In this field of therapy American investigators have blazed a new and important trial.

Burns:

Although the pathologic physiology of extensive superficial burns has in large part been known for many years, as was pointed out in the paper published in 1933, by J. Peyton Barnes, working under Dr. Singleton in this School of Medicine, the methods of treating these lesions have been many. The adoption of uniform methods in the treatment will lead to more rapid convalesence with less deformity than we had previously dreamed possible. A burn is a wound and it must be regarded as such. The more extensive the wound the more profound the physiological effects. It is generally agreed that 60 to 75 per

cent of deaths from burns are due to shock. Adkins who assisted in the treatment of the burned men evacuated from Dunkerque found that 60 per cent of the deaths occurred from shock and that this "is the most serious factor in burns."

We know now that we must prevent too great hemoconcentration, that it is easier to prevent it than to attempt to restore the normal level of concentration after severe plasma loss has taken place, for during the process of severe plasma depletion generalized capillary injury may occur. The burned area is highly susceptible to infection, and although the area is probably sterile immediately after the injury these lesions all too frequently become seriously infected. Finally convalesence is often too greatly prolonged and serious deformities too often are seen following these injuries. The availibility of enormous amounts of the blood substitutes for our armed forces, which has been made possible through the magnificent cooperation of the American Red Cross, will do much to prevent too great hemoconcentration and to restore a nearly normal level once hemoconcentration has occurred.

The adoption of the principles laid down by Allen and Koch, who suggested the pressure dressing method of therapy with the addition of a sulfonamide ointment as used by Dragstedt will have a profound influence on the results of these injuries which are frequently so devastating to our Naval forces. While the exigencies of warfare have made it necessary temporarily, at least, to use a tanning substance for burned surfaces other than the hands, face and genitalia, no one would predict that such substances, which without doubt detrimentally effect wound healing, will continue to be used. The sulfonamide pressure dressing method provides an efficient, safe, and sane basis of therapy. It meets the requirements of fundamental surgical principles in any method of the care of wounds and it, or some similar method will without doubt, be generally adopted.

Tetanus:

During the first World War there occurred a high incidence of tetanus in those wounded on the battlefields

of Western Europe. Tetanus antitoxin did not prove to be of very much therapeutic value once the disease was evidenced, but its use for prophylactic purposes was of definite value. The possibility that death in active tetanus is due to the presence of a secondary toxic agent formed from the primary toxin of the clostridium tetani, as has been suggested by the work of Abel, Shoemaker and Firos seems highly possible. This secondary toxin is not neutralized by tetanus antioxin. If these facts be correct, and there is every reason to believe that they are, some more active form of immunization must be provided.

Passive immunization with anti-tetanic serum has not proven to be a satisfactory procedure in military engagements. Of even greater importance is the fact that passive immunization with anti-tetanic serum lasts at most about ten days. The use of only a single dose is too frequently followed by severe reactions and succeeding doses increase greatly the incidence and severity of these disturbing and at times serious complications.

Active immunization with tetanus toxoid was universally adopted for the French and Italian armies and is used extensively in the Russian army. It has been adopted for our armed forces by the Surgeon-General of the Army and Navy. In the British army immunization has been on a voluntary basis, although 90 per cent of the British Expeditonary Force was immunized. Standards for the potency of each of the two types which are available in this country have been laid down by the National Institute of Health. With an adequate program of immunization, such as is now being used for our armed forces it is highly possible that this dreaded infection will not prove to be frequent or serious in our casualties.

France was the first to appreciate the value of toxoid immunization and her fighting forces and the horses belonging to these forces were immunized before the war begun. A single instance of tetanus developed and this did not prove to be serious. Following the British campaign on the mainland of Europe eight men are reported to have developed tetanus and these were all in a group of 1,800 casualties who had elected to omit toxoid injections. Of 16,000 who were also wounded, but who had

previously been immunized with tetanus toxoid not a single instance of tetanus occurred. The experience of the Italians is said to be similar to this and our own experience in a limited period of warfare, but in operations in many areas would point strongly to the fact that tetanus will not prove to be the scourge that it has been in all previous wars.

Conclusion:

These are but a few of the important advances in surgical therapy which will have a profound influence on the morbidity and mortality of the casualties in our armed forces. The reduction in the incidence of infection in wounds, and compound fractures by the use of sulfonamides will lead to earlier convalesence, and less deformity and mutilation than has ever been obtained in any previous war. The present program of toxoid immunization will lead to the nearly complete disappearance of tetanus among our injured men. The provision for large stores of adequate blood substitutes will permit our men to be treated before a fall in blood pressure presages that the serious state of shock is in full motion. Adequate nutrition will provide better surgical risks, earlier wound healing and perhaps some degree of visceral protection from some of the agents used in chemical warfare.

But sulfonamide therapy, and adequate amounts of the most efficient blood substitutes and the many other agents which are helping to provide a New Era in Military Surgery are to be considered merely as adjuncts to already accepted methods of treatment, for debridement and immobilization remain the essentials of the successful treatment of wounds. Nothing has been brought forward which will permit the surgeons of our armed forces to discard the fundamental principles of sound surgical practice, or to accept any compromise of these. Used together we can expect that the semi-permanent horrors of war, the deformities, the delayed healing of tissues, especially of bones, and mutilations which we have in the past been accustomed to associate with military casualties will be greatly reduced. During the World War I, 7.0 per cent of our casualties died, exclusive of those found dead on the field, while on Guadalcanal in this war

less than 1 per cent have died. The Russians using many of the therapeutic advances I have enumerated, report a death rate of 1.5 per cent of all casualties, exclusive of battle deaths.

But used alone without a realization of the many factors which influence infection, repair and homeostasis, the results would be disastrous. Under such circumstances the Officer will not have fullfilled Pare's dictum for he will not "seek all means for which the quick recovery of the patient" and even an injury "which may of its own nature, have been small, may by his negligence have become great."

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THE DOCTOR AND THE POST-WAR WORLD*

WITTEN B. RUSS

Our post-war difficulties cannot be solved by a materialistic approach to the problem of living. Food, housing, clothing and medical care, things that money and goods can buy, security furnished by the state will not suffice. Moral and spiritual leadership alone offer hope for our country in the dark and stormy days ahead. In every great crisis, the church and the medical profession, whose ideals of service before self and faith in love as the greatest power in the world, have kept the light on the hill, and have pointed the way to the heights from which even the humblest can see something of order and beauty in the universe. By precept and example they have urged man to strive for *strength* rather than for *help*. They have tried to make it plain that the way is easy and the burden light only for those who have wisdom to see the way, and strength to carry the burden.

Caring for the sick, comforting those who suffer pain is a noble calling. If you employ your talents to serve that end alone the reward will be a successful life. There is no security, no freedom from fear except through forgetfulness of self and service to others. The ecstasy that takes one beyond the power of anything to do him harm lies in sacrifice and in forgetfulness of self.

Over 800 years ago the greatest doctor of his time began his daily rounds with the following prayer:

"Grant that I may be filled with love for my art and for my fellowmen. May the thirst for gain and the desire for fame be far from my heart. For these are the enemies of Pity and the ministers of Hate. Grant that I may be able to devote myself, body and soul, to thy children who suffer from pain. Preserve my strength, that I may be able to restore the strength of the rich and the poor, the good and the bad, the friend and the foe. Let me see in the sufferer the man alone. When wiser men teach me, let me be humble to learn; for the mind of man is puny, and the art of healing so vast. But when fools are ready to advise me or to find fault with me, let me not listen to

* The Baccalaureate Address to the Graduates of the School of Medicine, University of Texas, Galveston, August 4, 1943.

their folly. Let me be intent upon one thing, oh Father of Mercy, to be always merciful to Thy suffering children."

The doctor, who is also a philosopher and a priest, will be needed in the post-war world as never before. While caring for the sick he will share the burden of trained scientists of the public health service in the prevention of disease. He must be skilled in both art and science. As a practitioner of the art of medicine, he need not be concerned with regimentation by the state nor need he worry about the passing of the doctor-patient relationship. Artists are never standardized. The family doctor who uses all his talents in the service of people who suffer from pain is always a happy and a successful man. He feels himself a hero and, after all, life is a failure for any man who does not feel that what he does is worth while.

It has been said that science takes life apart, philosophy puts it together again, religion gives it a meaning. The science of medicine is concerned with the prevention and treatment of disease which is important, but philosophy and religion are concerned with the patient who has the disease which is even more important. There is no beginning and no end of life. Thought of self alone creates the illusion that life begins and ends with the individual. This makes cowards of us all and robs us of human dignity. It also lowers our resistance to morbific influences in general, disturbs body chemistry in a way that confuses even the most astute scientist. The sick man needs all that science can give, but he needs much more than that. Terrified by the fear of death, he is unable to mobilize and use his natural body defenses. He is like a frightened child groping in the dark. He needs courage based upon the sustaining power of hope. If you are a real doctor, as well as a scientist, the patient will, in the darkest hour, put his hand in yours, and, together you will both find the light, his health restored, your power for good increased.

The doctor's leadership is not confined to the sick room. To be successful he must be a comforter, guide and friend. He must try to find what his patient thinks important, what he holds sacred and is willing to die for, and, always keep that in mind. He must not mistake the physical body for the man and allow pseudo-science to

blackout imponderables. Life is a mystery. Miracles with which we are confronted in our daily lives are so commonplace that we fail to recognize them.

I have a message to you from Dr. George Baehr, Chief Medical Officer, Office of Civilian Defense, the most important war activity in which we civilians are privileged to engage. Doctor Baehr is a scientist. But he is much more than that. He is a great doctor and a great leader. In cooperation with Public Health Service, Red Cross and the Armed Services, he is devoting himself, body and soul, to the great task of training and conditioning the civilian population to meet the strain incident to war. He says:

"In defense of the civilian population in time of war, the medical profession, the hospitals and the public health services of the country must be more alert to their responsibilities than ever before.

"As internes and as residents in hospitals you will soon be members of mobile medical teams, ready for service in any catastrophe, day or night. Many of you will then enter the armed forces of our country. Those who are obliged because of physical disabilities to remain behind after completing hospital training, must continue to do more than your share in shouldering the responsibilities of civilian defense in the communities in which you live. As members of the great profession of medicine your first thought should be public service, your last thought personal gain.

"During the war you will learn to think of yourselves as public servants. After this great war is ended all of you must be prepared in this same spirit to consecrate your lives to the task of reconstruction, if our Nation is to be rebuilt on a strong and enduring foundation."

Doctor Baehr is right. After this war, we must indeed learn to think of ourselves as public servants and consecrate our lives to the task of reconstruction.

What sort of a world are we to have after the war? What place will there be for the doctor when the state assumes care of the sick and seeks to make us all lodge doctors? What chance will you men have? In answer, I direct your attention to the doctors I knew in Texas when

I was a boy, with whom I began the practice of medicine over forty years ago. Many of them were without benefit of science and most of them were without much of the world's goods. All associated with publicans and sinners in the days when crime openly arrived at distinguished most parts of Texas. There were no places where doctors could find an easy environment. There were no hospitals, professional nurses, mechanical aids to diagnosis, and no specialists; not even an allergist, nor a pediatrician. It is interesting to know how doctors solved their problems in those days. I am sure you agree with me that everywhere, at that time, even in the desolate rural communities, the doctor was the leader and the happiest and most successful man in his community. The secret of it is, that he made his environment kind by the leadership he won through service alone. The faith that the humblest patients had in him, his ability to lift flagging spirits in the homes where even death had entered, the control he had over environment gave him a greater sense of security, than money or goods, or place or power could ever give. He treated the patient who had the disease rather than the disease that had the patient. He was a physician of the soul, a friend in the time of need. If, by chance, he reached old age, even the burden of the years was borne lightly and he was still a power for good, an example to those whose lives he influenced. He was loved and honored, because he was a great servant. After the war there will be no place for a doctor who is not a great servant.

Need I remind you that the heroes of the world, both saints and sinners, who have made progress towards what we call civilization possible, have seemed to rely solely upon that mysterious power called spirit. The power that performs miracles. Many of them have been out-laws and have worshipped strange gods. Most of them have been handicapped by poverty and even disease. They have come froms slums and desolate rural areas, but all have had faith in themselves and by that faith they have conquered. Mere brute force always loses in the end to the power of spirit. The bloody conqueror, Napoleon, in exile, admitted that spirit is always stronger than the sword.

Men are not wholly good, or, wholly bad. The concealed and often unconscious sins of the good and great are well known to you. The world had made heroes even of out-laws, if, in the long range view, they have contributed to progress. Time wipes out their bloody tracks; history weaves romance around their names; their motives are matched with their accomplishments; monuments are erected to their memories. We then realize that it was not by, but *in spite of brute force* and cruelty, that they became great.

The most influential life ever lived on this planet owed its power to spirit alone. So let us not forget that the chance for a happy and successful life depends solely upon faith that performs miracles. I hope you will never be tempted to exchange reliance upon that power for anything that the world has to offer. There is equal opportunity for all in the realm of spirit; opportunity to become strong and great through sacrifice of self in service to others; opportunity, as Doctor Baehr says, to consecrate our lives to the task of reconstruction. We must concentrate upon our duties and responsibilities. Seek to *be* something. We must earn our right to live. The world owes us nothing.

The future of our country, and of the world seems none too bright, but therein lies a challenge to the brave and self-reliant, who, somehow always find the way. Wiser men than you and I have been guided by a star. On the darkest night one can best see the stars.

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UNITED NATIONS HEALTH SERVICE

In the September 1943 *Free World*, Ludwik Rajchman asks why not a United Nations Health Service. He points out the world acceptance of the Postal Union and the Red Cross as examples by which a United Nations Public Health Service might be organized for international benefit.

Suggested fields of development for U.N.H.S. include an epidemiological field service, a colonial medical and health service, a central research service, and a public health commission.. The proposed epidemiological service might co-ordinate quarantine activities, assist in regulation of air-transport development to prevent epidemic spread, and to extend and amplify the work of such organizations as the Pan-American Sanitary Bureau, and the Inter-American Health Agency. A joint United Nations Colonial Health Service might co-ordinate health work of existing national services, and promote balanced health efforts all through colonial areas. A United Nations Health Service Research Institute might develop along the lines suggested by the National Institute of Health at Bethesda, Maryland. The Public Health Branch of the United Nations Health Service might include commissions for special co-ordination of public health efforts in various countries, central headquarters for public health training, and a center for collection and distribution of world health conditions.

Probably the most successful and lasting of all the efforts of the League of Nations, to which we actively contributed, was the Public Health Service, with the regular distribution of bulletins regarding health conditions all over the world. It would seem that the success of this work of the League of Nations would suggest the high probability of success of a United Nations Health Service, as proposed by Doctor Rajchman. *L. A.*

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POLIOMYELITIS:

Its Epidemiology and Measures for Its Prevention

L. L. LUMSDEN*

As yet the epidemiological verdict as to the causation and mode or modes of spread of poliomyelitis is a Scotch verdict—"not proven."

The public in general should be reasonably patient with the scientists engaged in the study of this as yet baffling problem because poliomyelitis as an outbreak or epidemic disease appears to be comparatively new. Hundreds of years passed after epidemics or pandemics of plague, Asiatic cholera, and yellow fever occurred as devastating scourges in different parts of the world before the causative factors and modes of spread of those diseases were definitely determined.

From the recorded history it seems probable that poliomyelitis occurred sporadically for many years before, but did not assume recognized epidemic proportion anywhere until about 1905. Between 1904 and 1916, endemics, outbreaks or epidemics with a total of over one thousand cases were reported in Sweden (in 1905 and 1911), in Norway (in 1911), in England (in 1911) and in New York (in 1907). The largest epidemic ever reported in one locality was that in the New York City vicinity in 1916. Why this disease or group of diseases gathered terrific epidemic momentum in the period 1905 to 1911 in a few regions or countries of the world is entirely unknown.

The specific causative agent is an ultramicroscopic filterable virus. The evidence of the specificity of the virus has been furnished mainly by experimental work on monkeys, some of which animals, upon having large doses of the infectious matter obtained from human cases introduced into them by intracerebral, subcutaneous, peritoneal, or intranasal inoculation or by feeding, develop a disease quite similar to poliomyelitis in human beings. Strains of the virus obtained from human cases in different outbreak areas present marked differences biologically, serologically, immunologically and otherwise. This fact suggests the possibility of there being several specific viruses

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of poliomyelitis instead of just one. Most of the laboratory experimental animals, other than monkeys and apes, such as guinea pigs, rabbits, rats, mice and birds, appear highly resistant against the disease. One strain of the virus, however, recovered from a human case a few years ago in Lansing, Michigan, has been found after passage through a series of monkeys to be capable of producing the disease typically and uniformly in cotton rats and, after passage through the cotton rats, in mice.

The virus has been found, as a rule, if the autopsy is conducted within a few hours after the death, in the spinal cord and brain of persons who have died with the disease, occasionally in the secretions from the nose and throat and more often in the feces from persons with current cases and from a small proportion of persons in contact with or in the vicinity of persons with known cases. Very interestingly, the virus during the last two or three years has been recovered in a few instances from city sewage and from collections of flies (mainly green or blue blow flies) captured in outbreak areas.

The mode or the modes of spread of the infection are unknown. Some of the leading so-called "authorities" on the subject, including especially some of the research workers in Sweden, New England and New York, at Johns Hopkins University and in the U. S. Public Health Service, have contended for years and continue to contend *(a)* that poliomyelitis is a strictly human disease spread entirely or almost entirely by contagion or by direct contact between persons, *(b)* that the sole or almost sole immediate source of the virus is the secretions from the nose and throat of persons with frank paralytic cases or with mild "abortive" (non-paralytic) cases or of persons who without manifesting any symptoms of the disease become carriers of the infection and spread it about for periods of days or weeks or possibly even months and *(c)* that there are in outbreak areas scores or, perhaps, even hundreds of mild abortive cases and carriers for every frank paralytic case. If the contention of these "authorities" is correct—and *possibly* it is—efforts to control the disease are and would be just about exactly hopeless. In a number of small localized outbreaks such as that connected

with a children's lemonade party in a suburb of Chicago and widely publicized in 1941, and another in the same year which was very intense and remarkablly localized in the Cordova vicinity in Walker County, Alabama, the chain of evidence presented by some of the investigators in support of their conclusion, or near conclusion, that the infection was spread through personal contact was impressive but, to some experienced observers, it was not convincing. In small communities with a high incidence of the disease it is difficult or actually impossible to eliminate mere coincidence having no bearing on the causation of the disease. If some new kind of skooter or bicycle for children were introduced suddenly into and distributed widely in a neighborly local community and a considerable number of broken bones occurred as a consequence, an epidemiologist would have no difficulty in tracing direct and indirect personal contact between some of the cases of broken bones during the two or three weeks prior to the accidents. Some of the instances reported in support of the contention that poliomyelitis is strictly and solely due to human harborage and transfer are remindful of comparable instances reported by authorities not many years ago in connection with the causation of typhus fever which now is established definitely as being due to insect-borne infection.

The finding of the virus of poliomyelitis in the secretions from the nose and throat or in the excretions from the gastrointestinal tract of certain persons does not mean necessarily that those persons are disseminating matter which is directly infective to other persons.

Other diseases, such as measles, diphtheria, mumps, whooping cough, smallpox, chickenpox, and so forth, definitely determined to be contagious behave differently from poliomyelitis. Multiple cases of poliomyelitis in a family are exceptional, while of diseases which are known to be contagious multiple cases in families or households are the rule. When two or more cases of poliomyelitis occur in a family they often have their onsets of illness within a period of twenty-four to forty-eight hours, which suggests a common source of and a simultaneous infection. In the temperate zones the acute diseases definitely es-

tablished as contagious generally have their high rates of prevalence in the late fall, the winter and the early spring, while poliomyelitis is very largely a disease of summer and early autumn. The seasonal prevalence of poliomyelitis is quite similar to that of yellow fever, dengue, typhoid fever and dysentery.

The geographical distribution of outbreaks of poliomyelitis is one of the most striking epidemiological features of the disease. In some outbreaks it is widely and thinly spread over large urban and/or rural areas. In others it is remarkably localized—in some instances the outbreak incidence being confined to one—a larger or lesser—part of the area of a large city. In the epidemic in the southeastern section of the United States in 1935 the outbreak incidence was confined to two adjacent groups of counties—one in the north-central part of North Carolina and one in the south-central part of Virginia—and to a group of counties in the western part of Kentucky. The epidemic in the United States as a whole in 1936 was remarkably confined to one region comprising the northwestern part of Alabama, the northeastern corner of Mississippi and a single tier of counties adjacent to the Alabama-Mississippi outbreak area extending from the south to the north border of Tennessee. In the present outbreak beginning in the early part of June, 1943, in Houston, Texas, the greater part of the city's area and population is involved, with cases by place of residence scattered about therein, but one large area with an estimated population of 100,000, including many families of shipyard and other industrial workers and of Mexicans and negroes, in the northeastern section of the city north of Buffalo Bayou and east of Main Street has remained to date, August 20, exempt from the outbreak. In this northeast area only two cases have been reported in the period of the outbreak, an incidence less than that of the average for the city as a whole during the past seven years. In each of these two cases the diagnosis was definitely doubtful and the epidemiological evidence is strong that if either or both of them were poliomyelitis, the infection was contracted in some other section of the city or during visits to places outside the city. The ages of these two

persons with doubtful cases were thirty-two and sixteen years, respectively. In the other areas of the city with an aggregate population of about 320,000 the incidence in the current outbreak has been 1 to about 5,800 of population.

Large cities in the same general region and closely connected by heavy human travel and traffic with a city stricken with a severe outbreak often remain exempt. Such geographical distribution does not appear to square with the contention that poliomyelitis is strictly a human harbored contagious disease.

Some of the long-time profound students of poliomyelitis have concluded that the infection is harbored by rats and is spread from them to man by fleas as has been determined to be true for bubonic plague and (murine) typhus fever.

About thirty years ago research workers in Harvard University and others in the Hygienic Laboratory of the U. S. Public Health Service reported that they had succeeded in transmitting poliomyelitis infection from monkey to monkey through exposure of the monkeys to bites of stable flies captured in the markets of Boston and Washington, respectively. Their reports caused a considerable wave of scientific enthusiasm. They and others reported, however, from repeated subsequent experiments with stable flies raised from the eggs under laboratory conditions entirely negative results. Then the scientific pendulum swung away—perhaps too far away—from biting insects as vectors of the infection.

The epidemiological behavior of poliomyelitis usually is very different from that of typhoid fever and other infections known to be excreta-borne. The fact alone, however, does not preclude the possibility that poliomyelitis is due largely to excreta-borne infection.

The finding of the virus in flies captured in outbreak areas is impressive but not yet epidemiologically convincing.

Considerable epidemiological evidence has been collected pointing to the possibility that birds and fowls may be an important harborage of poliomyelitis virus as appears almost certainly to be the case with the viruses of

eastern and western equine encephalitis and of St. Louis encephalitis.

The different epidemiological behaviors of different outbreaks of poliomyelitis suggest the possibility—or even the probability—that in this problem we are dealing with two or more diseases—clinically and pathologically quite similar—caused by specifically different viruses spread in different ways.

Preventive Measures—In view of the uncertainties as to the causation and the mode or modes of spread, a satisfactorily definite and specific prescription for the control or prevention of poliomyelitis cannot be written. However, with such epidemiological facts as we have about the disease and by applying the rules of common sense, the following measures for a community stricken with an outbreak or epidemic of poliomyelitis may be prescribed with a fair degree of assurance:

1. Clean up and stay clean!

As fecal matter from persons appears as yet to be the most frequent possible source of the infection, the clean-up should be applied vigorously and promptly to insanitary deposits of human excreta and to procedures to prevent excretal contamination of any matter likely to be conveyed to the mouths or to the subcutaneous tissues of persons. Insanitary privies should be abolished and replaced with sanitary privies or, better still, with properly equipped and properly sewer-connected water closets as soon as practicable. All privies and cesspools which cannot be abolished promptly should be treated immediately and thereafter once every two weeks with a strong disinfectant solution—one pound of fresh chlorinated lime or one-half pint of cresol well mixed in about two gallons of water being applied to the privy contents and to the soiled parts of the privy structure.

2. A systematic, intense and continuing fight on rats, mice, flies (especially blow and house flies), mosquitoes, roaches, fleas, bedbugs, ants and other pestiferous and dangerous insects and vermin (including English sparrows which are dirty, lousy birds and properly may be designated "flying vermin") in their breeding, lodging and eating places. This is warranted because it is by no

means yet proven that in some outbreaks lower animals do not harbor and insects do not transmit poliomyelitis infection.

3. Systematic, continuous and rigid sanitary and hygienic collection and disposal of garbage, stable and pen manure and excretal droppings from poultry and birds.

4. Screenings and other measures to exclude, to the highest degree practicable, insects and vermin from living, sleeping and eating places used by persons.

5. Provision of adequate clean or purified water-supplies and, to the fullest extent practicable, sanitary sewerage systems with proper operation of proper facilities for sanitary final disposal of city sewerage.

6. Adequate rigid official inspection to insure the maintenance at all times of sanitary and hygienic conditions in public eating and drinking places—including thorough cleansing and sterilization with heat or chemicals of eating and drinking vessels and utensils before each use of them. This is important because some persons apparently perfectly well going about in the community may be carrying the poliomyelitis virus in their noses and throats.

7. A publicity educational campaign to discourage unnecessary spread of potential droplet infection through unhygienic coughing, sneezing, spitting, blowing and wiping.

8. Restriction to a reasonable degree of travelling, visiting and attending public assemblages by children under six years of age.

9. Restraining young children from undue physical stress. Fatigue is supposed by some students of the problem to increase the chances of development of high suceptibility to the disease.

These measures according to all of the epidemiological evidence we yet have are the most likely to be effective in the prevention and control of poliomyelitis infection. They are in line with the advice of the good old country doctor, who said to his younger colleagues: "When you prescribe, be sure your medicine will do no harm."

These measures are for the eternal good of the community—physically, mentally and spiritually. Even if they had no considerable effect in the prevention of poliomye-

litis, they are highly effective in the prevention of many gastrointestinal and respiratory infections which together are likely to cause in our average community more sickness and death in one or two years than poliomyelitis will cause in ten or even a hundred years.

Running away from outbreak areas is not likely to have much advantage. Trying to run away from poliomyelitis is comparable to trying to run away from lightning stroke. No one can forecast where it is going to hit next.

Closing of schools, churches, theatres and hygienically operated swimming pools, as often is demanded by misled public opinion, is unjustified. Opening schools on schedule or keeping them open is advantageous because in the schools the children are under observation—which easily can be made skilled observation—and the chances are augmented for early diagnosis and treatment of cases among the children, and also for finding cases in families of absentees from school.

Placarding of the affected homes is advisable, because in some instances poliomyelitis appears to be caused by infection of place rather than by persons.

Proper isolation of patients with the disease is advisable especially for protection of the patients against some other current infection and also against unenecessary social disturbance and agitation. There should be rigid disinfection of discharges from the intestinal tract and of those from the nose and throat.

Quarantine or exclusion from work of adult members of affected families excepting those engaged in the handling of public foods or in work which brings them into close contact with many young children, is unwarranted and often causes unnecessary serious hardship.

Marked progress has been made in recent years in procedures for treatment of the disease. The improved methods of treatment appear definitely to have lessened much of the pain and discomfort in the acute period of the disease and also—and highly important—the likelihood of resultant permanent paralysis from the disease.

Though difficult to be philosophical under such cirstances, the parents of a child with permanent paralysis

resulting from poliomyelitis have fair reason not only to hope but also to expect that the child, because of physical deprivation, may be stimulated to increased mental activity with augmented intellectual development as a result. Some of the greatest producers of literature, art, and science have been physically handicapped.

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CENTRAL NECROSIS IN UNCONTROLLED GROWTH

A neat analogy may be made between the growth of a city and the growth of more conventionally considered multicellular organisms. If growth is harmonious and balanced,—controlled in other words,—there is health, with wide open arteries for transport and traffic, and without overcrowding or congestion. When growth becomes uncontrolled, with resulting congestion, inevitable central necrosis and decay sets in. All values are lost as the area disintegrates. The more rapid and uncontrolled the growth at the periphery, the more wide spread does the cancerous central necrosis become.

It is interesting that this significant pathological analogy was first appreciated by the distinguished Finnish architect and civic engineer, Eliel Saarinen (*The City: Its Growth; Its Decay; Its Future,* New York, 1943). Saarinen indicates that the treatment of such conditions might profitably follow medical examples, by drastic surgical removal of the cancerous growth, and by attempts at more controlled and orderly development.

There are important philosophical implications in the analogy. Perhaps the same basic factors which relate to the biological growth of multicellular organisms relate also to the development of communities of humans. If so, perhaps physicians might profitably study growth factors in preparation for consultation on community planning. Saarinen's contribution from famed Cranbrook Village in Michigan might be a worthy volume for beginning this study.

—*C. D. L.*

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NEUROSYPHILIS*

JACK R. EWALT

The early history of syphilis was buried with the tribal medicine men and the witch doctors of the western hemisphere, and they left no known written records. The recorded history of syphilis begins with its importation from the new world to Europe by the crewmen of the Columbian explorations in about 1493. The initial papers were symptomatic descriptions and the etiology was ascribed to factors varying from the influence of the moon to the curse of the devil, but was rarely ascribed to sexual promiscuity.

The first reports mentioning involvement of the nervous system appeared approximately 19 years after the first European epidemic, which approximates the average incubation period for general garesis in untreated syphilis. The early authors apparently suffered from the infection themselves. A partial translation of one report is contained in the historical resume of Moore and Solomon (1). "In certain cases the brain in the end became infected. Tremblings of the hand, the feet, and the whole body set in; the tongue was impeded and babbled. From this time on there was no hope. The disease was incurable."

These earliest authors point out that syphilis is a generalized infection involving the entire body and that it can produce symptoms in any or all the body systems. This fact, though noted by the first writers on the subject, is too often overlooked or momentarily forgotten by modern specialists treating one or another phase of syphilis. While general paresis was long suspected of being due to syphilis involvement of the brain, it remained for Schaudin and Nogacuhi to demonstrate the spirochetes in the brains of patients suffering from dementia paralytica. The introduction of the Wassermann test gave a reliable method of confirming the clinical diagnosis.

The best early description of the syndrome of general paresis is the monograph of Emil Kraepelin (2). He described the symptoms presented in many modern textbooks,

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and classified the patient, according to symptomatic variation, into demented, depressed, expansive, and agitated forms. He introduced the term "galloping paresis" as a subtype under the agitated form. He states, "Perhaps a better knowledge of the etiological or the pathological—anatomical relationships of the disease will enable us, under a new point of view, to evolve a more reliable grouping." Kraepelin described the course, noted the presence of remissions, and remarked, "The termination of paresis is regularly death." He stated that approximately half the paralytics died in two years and almost all within five. The fact that some factor other than syphilis itself must operate to produce the infection in the brain in some individuals and not in others was noted, and the influence of alcohol, the color of the skin, climatic factors, racial factors, and the mode of life of the individual person were discussed extensively. Krafft-Ebing's theory of the etiology of dementia paralytica, which he summarized as, "syphilization and civilization" is also discussed in this monograph. Kraepelin observed that the course of general paresis was favorably influenced in certain patients by purulent conditions, induced by rubbing the scalp with a tarter emetic salve or rubbing the scalp with a bone, and mentions the favorable influence of tuberculin injections on the course of neurosyphilis. He failed to note, or at least he did not mention, that all of these agents are pyretogenic and he apparently made no observation as to any correlation between the results obtained and the febrile reaction produced by the various therapeutic agents. As is true of most Kraepelinian psychiatry, emphasis is placed on accurate description of clinical types and little attention or interest given to therapeutic possibilities.

It remained for Julius Wagner-Jauregg (3) to introduce therapeutic malaria, for Jacobs and Heidelberger (4) to synthesize tryparsamide and for Loevenhart and his associates to demonstrate its use, before any effective therapeutic weapons were available. The present problem of syphilogists in relation to neurosyphilis is three-fold. First, and most important, is prevention by the isolation of infectious syphilitics and by adequate treatment of these infected persons. Second, the early recognition and energetic treatment of syphilis of the nervous system before the dam-

age has become irreparable, and third, the development of more efficient agents for treating the infected person.

GENERAL RESUME

The discussion in this present series will be confined entirely to syphilis of the nervous system, but as was previously mentioned, syphilis of the nervous system is but one phase of a generalized systemic infection. The literature abounds with learned discussion devoted to a consideration of why some syphilitics develop an infection of the nervous system while others do not. Dunlap (5) has given an excellent discussion of the distribution of spirochetes in the brains of general paretics and discusses the possibility of the existence of neurotropic strains of the organism as first suggested by Levaditi and Marie. He also discusses Ehrlich's proposition that the spirochete adapts itself to the host over a period of years and following this period of selection and adaptation is able to invade the nervous system. Menninger and Grotjahn (6) offer further evidence of the neurotropic strain in that they found a positive history of neurosyphilis in 36% of the families in their juvenile paretic patients. They also collected a large number of patients in which two or more members of the same family had neurosyphilis of the same clinical type. These authors also mentioned the relatively frequent occurrence of conjugeal paresis or tabes and present a small group in which three or more children in the same family are all afflicted with juvenile paresis. Further evidence is presented by Hutton (62) who found neurosyphilis in 48% of the syphilitic infected consorts of a large group of cases under his care.

The older studies reveal an incidence of neurosyphilis infection in only 5% to 10% of all syphilis patients, but these figures are perhaps a reflection on the adequacy of the diagnostic studies made. It is not logical to assume that the central nervous system is infected to any less degree by syphilis, a systemic infection, than the cardiovascular system, even though neither may show any symptoms or signs ascribable to syphilis at the time of a particular examination. More careful studies have prompted workers such as Kemp and Menninger (7) to make statements that 80% of syphilitics have some central nervous system involvement at some time. The Cooperative Clinical Study on Asymptomatic Neurosyphilis (8), in a survey of 5,293 patients who had

at least one spinal fluid study during the course of the infection, found that 53.4% of the cases had positive spinal fluid serologies and 39.9% of the patients with positive serologies had associated clinical signs of neurosyphilis. This suggests that an even higher incidence of involvement of the nervous system will be found as laboratory and clinical examination techniques become more precise and as the educational program brings about a more generalized use of these methods. The reason that syphilis becomes clinically manifest in the heart, the liver, the brain, or the spinal cord in certain patients is not known. The old theory of a "zone" or "area of minor resistance" is merely a verbal fog to shield our areas of ignorance. While the above mentioned studies on neurotropism are interesting they remain scientifically unconvincing and further researches are required. One is tempted by the similarity of the cord symptoms in tabes and pernicious anemia to postulate the possibility of a deficiency state as the physiologic condition which permits or aids the spirochete in bringing about structural changes in the posterior column. The cord changes in pernicious anemia are felt to be due to a vitamin B1 deficiency by the more fashionable members of the vitamin hierarchy, although the actual role of thiamin deficiency in either combined degeneration or tabes is still largely speculative. With the popularization of more accurate diagnostic methods there has been an apparent increase in the incidence of neurosyphilis. The fact that more cases of neurosyphilis were diagnosed and reported during the decade following the introduction of the arsphenamines has encouraged various theories that neurosyphilis is precipitated by antisyphilitic treatment and certain individuals have stated that the incidence of neurosyphilis is increased by the use of arsenicals in the treatment of early syphilis. These studies fail to take note of the fact that the widespread application of the diagnostic procedures necessary for the detection of neurosyphilis, did not appear until the decade following the development of the arsphenamines by Ehrlich. The Cooperative Clinic Study has attempted to evaluate the role of treatment on the incidence of neurosyphilis (8). Asymptomatic neurosyphilis was noted among 7½% of the patients who had a minimum of 20 injections of the arsphenamines and 20 injections of the heavy metal given as a continuous

course. The incidence of asymptomatic neurosyphilis was 22.6% in those patients who received approximately the same total amount of treatment administered irregularly, with lapses and rest periods. "Further evidence in support of the conflict that modern treatment of early syphilis does not predispose to the production of asymptomatic neurosyphilis—shows that the patient treated continuously and adequately during the first two years of the disease developed a lower percentage of symptomatic and asymptomatic neurosyphilis than those treated continuously, but given an inadequate amount of treatment." Further figures are presented which show that of those syphilitics who receive no treatment, 55.6% eventually develop symptomatic neurosyphilis while those who were adequately treated only 38.2% developed symptomatic neurosyphilis. One of the preliminary reports of the Cooperative Clinic Group (9) for a study of non-specific treatment of neurosyphilis reveals that patients treated during the early stage of syphilis respond to treatment of neurosyphilis better than patients who were not treated in the early stage. Moore and Hopkins have reported that the average incubation period of general paresis is 19 years in patients untreated for early syphilis and 15 years in patients receiving treatment. It has also been shown that syphilitic meningitis, a rare disorder in the United States, occurs approximately 10 times as often in inadequately treated early syphilitics as in those receiving no treatment. In spite of the tendency of inadequate early treatment to shorten the incubation period of general paresis, any treatment at all in the early stages of syphilis decreases the probability of a neurosyphilitic involvement and renders the infection more amenable to treatment in those individuals who do develop neurosyphilis. The incidence of neurosyphilis is of course very much lower in patients who have had adequate treatment for early syphilis. There are no statistically reliable studies of the incubation period of neurosyphilis in patients treated by modern intensive continuous methods, because these methods have not been in use long enough to cover the ordinary span of years necessary for the development of the full number of neurosyphilitics to be expected.

TYPES OF NEUROSYPHILIS

It has been previously stated that syphilis of the nervous

system is part of a generalized infection and accordingly all parts of the nervous system may be presumed to be infected in spite of the fact that we are unable to demonstrate the infection in many instances by present diagnostic methods. For purpose of organization in the discussion it is customary to divide neurosyphilis into various types and in this discussion we will use the classification of Joseph E. Moore because of its simplicity and general utility. Moore groups neurosyphilis as follows:

a) Asymptomatic neurosyphilis
b) Meningeal neurosyphilis
c) Vascular neurosyphilis
d) Diffuse meningovascular neurosyphilis
e) Parenchymatous neurosyphilis.

The above symptomatic classification denotes the area of the nervous system in which the major damage is manifest.

SYMPTOMATOLOGY

I. Asymptomatic neurosyphilis.

Asymptomatic neurosyphilis is that form of syphilis of the nervous system manifest by a positive spinal fluid serology and without clinical findings ascribable to syphilis. It is to be presumed that the examination for clinical signs will be completely and carefully done before such a diagnosis is made. As was noted in Section B, the incidence of asymptomatic neurosyphilis decreases with the adequacy of the treatment of the early syphilis. The sub-classification of asymptomatic neurosyphilis is based entirely upon the degree of involvement of the serology and has been divided into four groups by the Cooperative Clinic Study (8) and into three groups by Moore (10). Groups 2 and 3 of the Public Health groups correspond approximately to group 2 of Moore. These groupings are characterized by the following laboratory findings:

Group I: Cases in which the lymphocyte count is 10 or more cells, with or without a positive globulin test: The Wasserman and colloidal tests are negative.

Group II: Cases in which the cell count and globulin content are normal or increased; the Wasserman test is positive, and collodial tests are indeterminate or positive, if the latter, usually being of the syphilitic zone type.

Group III: Cases in which the cell count is 30 or more, the Wasserman test 4 plus, and the collodial curve negative or of the syphilitic zone type. Patients falling just short of Group IV are also included in this group.

Group IV: Cases in which the spinal fluid shows the so-called paretic formula, i.e., marked excess globulin, strongly positive Wasserman (0.2 cc. or less), and the paretic type of collodial curves. The Cell count is above normal and contains, in addition to small lymphocytes, large lymphocytes and polymorphonuclear leukocytes." Inasmuch as the diagnosis of this condition is based entirely on the detection of spinal fluid abnormalities, the question of the best time for examination of the fluid is important. The optimum time for this examination varies with the stage of syphilis.

(a) Early syphilis. Both Moore and The Cooperative Clinic Group recommend testing of the sqinal fluid by the sixth month of treatment in early syphilis. If the fluid is negative, it need not be repeated until the end of the course of treatment. If the examination revealed a positive fluid it should be repeated every three months to observe whether the trend is progressive or toward improvement. A serologic relapse in the blood during the course of active treatment is an indication for spinal fluid examination. Patients who take treatment irregularly should have the spinal fluid examined periodically at least each six months. Any patient showing any symptoms or signs of involvement of the nervous system such as headache, dizziness, visual disturbances, etc., should be immediately examined for spinal fluid abnormalities. The spinal fluid should be checked finally in all cases before they are placed on their period of rest or observation after completion of their continuous intensive course of treatment.

(b) Late Syphilis. All patients suffering from late syphilis should have a spinal fluid examination. If this examination is negative it is stated that 99% of them will remain negative providing the patient takes adequate treatment. Patients with late syphilis who have a negative spinal fluid in the initial examination and who report faithfully for their treatment will not require a re-examination unless they develop clinical signs of involvment of the nervous system. Patients who show a positive spinal fluid serology when first

seen, should have repeated examinations at intervals of not less than six months or upon development of any clinical sign of progression of the disorder. Any tendencies toward progression is an indication for institution of a more vigorous type of therapy. The type of treatment and the results to be expected will be discussed in the section on therapy. Any progression of symptoms will result in some one of the forms of neurosyphilis to be discussed below or in some combination of these forms.

II. Meningeal Neurosyphilis

1) Acute syphilitic meningitis.

The clinical picture in this syndrome is essentially the same as that due to meningitis from any cause. It is within this group that inadequate early treatment may precipitate the disorder. Stokes has stated, "It is merely a relapse of an imperfectly extinguished infection in a structure peculiarly inaccessible and difficult of sterilization and in a patient whose resistance has been prevented from developing by improper treatment." Syphilitic meningitis has been shown to be approximately 10 times as common in patients who are inadequately treated for early syphilis as in patients who receive no treatment at all. Grinker (11) has stated "Clinical experience has proven that mild or absent skin lesions in the secondary stage usually means severe neurosyphilis. On the other hand, severe skin lesions seem to prevent the development of the malignant types of neurosyphilis. It is possible that the skin, an epidermic structure, when infected produced antibodies in sufficient quantities to protect the other great epidermic tissue, the nervous system."

Merritt and Moore (12) have an excellent monograph on acute syphilitic meningitis. They have found the reports from the literature to show a variation from .2% to 5% of cases of early syphilis who develop meningitis. Syphilitic meningitis may occur during any stage of syphilis, although in the majority of incidences it occurs in the early stages. In may occur at any age and there is no particular racial distribution. It frequently occurs in patients who lapse from treatment of early syphilis and it may be that the above quoted statement of Grinker has a special application in this form of neurosyphilis. It is extremely uncommon in patients who have had as many as 15 injections of some

arsphenamine and the obvious prevention of this disorder is adequate early treatment of syphilis with enforced treatment if the patient fails to co-operate. Merritt and Moore classifly their acute cases into three groups presumably on the basis of variations in pathology. Their grouping makes a convenient way of dividing the patients smyptomatically. (1) Acute Syphilitic hydrocephalous. This is characterized by nausea, vomiting, stiff neck, and choked disc. The author feels that this is probably due to major involvment of the posterior fossa with impairment of the circulation of the spinal fluid; (2) Acute syphilitic meningitis of the vertex. In this form, the symptoms are largely irritative phenomena and include convulsions, focal symptoms such as hemiplegia, aphasia, etc., in addition to rigidity of the neck, postive Kernig sign, headache, and occasional nausea. (3) Acute syphilitic meningitis, basilar type. This is the most common variety and includes the symptoms outlined above plus involvement of one or more of the cranial nerves. The serologic findings are typical. About 60 per cent of the cases have a positive blood Wasserman and most of the others give a positive history of syphilis. The spinal fluid findings reveal pressures ranging up to 600 millimeters of water, a cell count varying from 100 to 2000 cells, with 80 to 90% lymphocytes. The globulin reaction will be positive in most cases and the total protein will be increased. The collodial gold curve will usually show an elevation in the first or second zone although in some cases it will be negative. The spinal fluid Wasserman is positive in about 90% of the cases. Sugar and chloride components of the spinal fluid will show no significant variations from normal. The spirochete has been demonstrated in the fluid but this is a difficult technique and its absence is of little value in diagnosis.

The differential diagnosis is chiefly concerned in distinguishing between meningitis due to syphilis and other forms of meningitis, in order that proper treatment may be instituted. Purulent meningitis and meningococcic meningitis are characterized by a higher cell count, usually ranging above 10,000 cells, most of which are polys. The presence of bacteria in some of these polys is another valuable differential sign. A positive Wasserman in the blood may be of aid in differentiating, but it must be borne in mind

that syphilitics are not immune to the other forms of meningitis and careful differential studies must be made. Tuberculosis meningitis is the most difficult differentiation to make because the spinal fluid cell count and differential picture is approximately the same. In tuberculosis meningitis a pellicle is usually formed on fluid which is allowed to stand immediately after withdrawal. Such pellicles will rarely form if the fluid is carried around in the errand boy's pocket before coming to the laboratory. Stained smears from the pellicle and from the centrifugal fluid will usually reveal the acid fast bacillus in tuberculosis meningitis. The spinal fluid chloride is rarely below 625 milograms in syphilitic meningitis while it is customarily lower than this in the tuberculosis form. In the latter type of meningitis there is usually a history of tuberculosis preceding the onset of the meningeal irritation. Torula is an extremely rare disorder but when it occurs the initial differentiation may be difficult because the spinal fluid Wasserman is frequently weakly positive due to non-specific reaction. Culture for the yeast bodies and the presence of the infected sinuses about the body are the most helpful differential signs.

2) Chronic syphilitic meningitis. This may occur as the primary picture or as a complication in improperly treated cases of the acute form. The symptoms are probably due to an unresolved exudate with the formation of adhesions as well as the infectious process itself. The symptoms vary according to the area of the brain covered by the most seriously involved meninges. There is usually a constant, sharp headache, some apathy, vertigo, and vomiting. There may be sensory changes or motor paralyses or aphasias depending upon the areas involved. An interesting symptom is tenderness upon percussion over the skull when the involved area lies under the vertex. Basilar involvement is common, often giving rise to adhesions, and according to some workers these adhesions may involve the optic chiasm producing a complete or partial optic atrophy. Other cranial nerves may be involved; the third, fourth, and sixth, are most commonly afflicted and a great many ocular palsies are due to chronic syphilitic meningitis. Gummatous meningitis is described in some texts. It is a rare disorder and cannot be clinically differentiated from chronic syphilitic meningitis. In some instances the gummas are reported to become of large size

and to produce tumor symptoms. In practice glioblastoma and brain abscess in individuals suffering from neurosyphilis, are more frequently found than gumma of the brain. Hypertrophic meningitis of the spine is merely a form of chronic syphilitic meningitis involving the meninges around the cord and producing symptoms according to its area of location. It is most commonly found in the cervical region where it produces root symptoms and may produce sensory changes in the ulnar and median nerve distributions. If it progresses, it may produce, through involvement of the motor roots to the brachialplexis, bizarre atrophies and paralyses of muscles in the upper extremities, in individuals who show no neurologic abnormalities below the level of the cervical spine. The process may progress or may include gumma formation with signs of progressive pressure on the cord.

III. Vascular Neurosyphilis

A case of purely vascular neurosyphilis never existed but in some patients the outstanding clinical findings are due to vascular involvement and for ease in discussion it will be described as a single entity. The classifications of vascular neurosyphilis are almost all based on pathological findings and they cannot be clinically differentiated. Grinker (11) uses Jakob's classification dividing them into (1) Huebners endarteritis (2) Chronic leutic vascular disease (3) Leutic arteriosclerosis and (4) Leutic endarteritis of the small cortical vessel. Vascular neurosyphilis frequently accompanies cardio-vascular syphilis and is merely part of a widespread involvement of the vascular system. Burnett and Rymer (13) found that 33.9% of a group of 215 cases of neurosyphilis, most of whom had a diagnosis of general paresis showed involvment of the cardiovascular system as manifest by the clinical findings or X-ray evidence of aoritis. Electrocardiographic findings were not included as these findings are not specific for neurosyphilis. The symptoms of vascular neurosyphilis are usually due to the diffuse endarteritis with a resultant ischemia of the brain. This usually produces a dull, diffuse headache during the acute stage with irritability and occasional attacks of convulsion, aphasia, or hemiplegia. These latter symptoms may be transitory in nature, and incomplete or transitory hemiplegia, in the absence of hysteria or arteriosclerosis,

should make one suspicious that vascular neurosyphilis exists. As the condition progresses one may have areas of softening and more permanent focal signs appear. These signs usually come on slowly and may require from a few hours to several days before they are fully developed. The patient will often remain conscious during the period of development of the symptoms and may occasionally awaken in the morning feeling well only to find that he has a hemiparalysis. Small miliary aneurysms are occasionally found, but contrary to popular belief, rarely produce hemorrhages. The syndrome of spontaneous subarachnoid hemorrhage is rarely due to syphilis. An involvement of the basal ganglia by the endarteritic process may produce a paralysis agitans like syndrome which has been called mesencephalitis leutica by Grinker and which has been described by Mella and Matz (14). The differential is usually made by the presence of the Argyle-Robertson pupil and the positive spinal fluid Wassermann.

Certain individuals suffering from syphilis may develop a transverse myelitis. The signs are those of transverse myelitis due to any other cause and consist of a loss of motor power and loss of cutaneous sensation in the lower extremities. The tendon reflexes, plantar reflexes, etc. are absent. Sphincter control is usually gone and decubitus ulcers soon appear. There is usually an elevation of temperature to 101-102° F. (R), and in the intial phase the patient appears ill. The course varies, some cases remaining stationary, some improving and some progressing upward and causing a respiratory death. The progress may be checked from day to day by marking the sensory level on the skin of the trunk. Patients who develop an associated atrophy of the optic nerve usually progress to a fatal termination. An occasional patient, with no other signs of neurosyphilis, will suddenly develop a myelitis a few minutes or hours after an injection of one of the trivalent arsenacles. The symptoms, signs and course of these cases are no different than those known to have neurosyphilis, although the onset is usually more rapid.

IV. Diffuse meningovascular neurosyphilis

This is numerically the largest and symptomatically the most heterogenous of all the forms of neurosyphilis. The symptoms may consist of any one or several of the

symptoms described under chronic meningeal syphilis plus any or all of the vascular phenomena discussed in group III. In general, the symptoms are characterized by headaches, dizziness, convulsive phenomena, aphasias, cranial nerve palsies, irritability, defects in memory and a general dulling of the intellectual processes. Vascular accidents may occur. Hemiplegia is a common symptom and may be the initial complaint in this disorder. The hemiplegia usually develops slowly, as described under vascular syphilis, and is sometimes a transitory phenomena, although in many instances some residual defects persist and in some cases a permanent paralysis results. 10-15% of untreated early syphilis patients will develop diffuse meningovascular syphilis. The period between primary infection and the onset of meningovascular symptoms varies from 1-20 years although the average patient will show his first symptoms in 8-10 years after the initial contact with the disease. The incidence of this form of neurosyphilis is greatly reduced by even inadequate treatment of early syphilis. Adequate treatment of early syphilis reduced the incidence of meningovascular neurosyphilis to an insignificant figure. There is no evidence to date that inadequate treatment of the early phase of the infection significantly shortens the incubation period, as it is thought to do in general paresis, Moore reporting a difference of only three years in the untreated and treated groups. The pathology varies with the extent and type of involvment. The vascular picture is predominantly one of endarteritis. The brain parencheyma may show areas of ischemia or softening. Actual hemorrhages are rather rare and tend to be small. The meningeal picture is one of adhesions and thickening. The serology in the blood is positive in only 65-70% (15) of cases before treatment and in a much smaller percentage if treatment has begun before the tests are made. The spinal fluid will be positive in approximately 90% of untreated cases but here again any treatment at all of the early syphilis will result in a smaller percentage of positive fluids in patients with clinically manifest meningovascular syphilis. Each case must be considered individually with careful study of the history and the findings in all the physical, neurologic, mental and laboratory examinations. Cerebral arteriosclerosis is the disorder which most frequently obscures the picture and must be differentiated because

it too is characterized by signs of cortical irritation plus signs of vascular inadequacy. In general, cerebral arteriosclerosis develops in a later age group (usually 60-70 years) but this differential may be misleading in patients contracting syphilis late in life or in young individuals with a tendency to angiospasm. The spinal fluid examination, and the finding of confirmatory signs of retinal and generalized arteriosclerosis are probably the most reliable differential signs. The history of and signs of cardio-renal pathology also aids in making a differentiation. Brain tumor is usually differentiated by the insidious onset and associated neurologic signs. It should be borne in mind that neurosyphilis patients occasionally develop brain tumors, which are, unfortunately, usually diagnosed at the post-mortem table.

V. Parenchymatous Neurosyphilis: including

a. General Paresis
b. Tabes Dorsalis
c. Atrophy of the Optic Nerve

a. General Paresis: (Dementia Paralytica, Meningoencephalitic syphilis)

"General paresis is an organic brain disease, always due to syphilis and marked by serological findings which are almost absolute in diagnostic value; by neurological signs which are quite reliable and by mental findings which are more or less characteristic" (16). This form of neurosyphilis accounts for at least 10% of all admissions to the public mental hospitals of this country. It is the most malignant form of syphilis and prior to the development of modern treatment methods it almost invariably resulted in death. In spite of the most modern and energetic treatment, about 30% of persons developing this disorder show no improvement and the bulk of this refractory group ultimately die of the disease.

The interval between the primary lesion and the development of clinical signs may vary from 8 months (17) to 30 years, but the average interval is about 15 years. Cheney (18) observed that 57% of cases came on after latency period of 10-19 years, 6% in over 30 years and less than 2% in less than 5 years. Kraepelin (2) observed that nearly one-half of untreated patients die within 2 years after the development of symptoms and almost all are dead within 5 years. Patients suffering from so-called "galloping

paresis" may die within 2 or 3 weeks (19) while Galbraith (20) and others have reported untreated patients living 30 or more years after symptoms develop. The average age of onset is about 40 years, 70% (18) of cases developing in the third and fourth decades of life. What circumstance or combination of physiologic functions permits the organism to remain dormant for so many years and to then become active in the brain remains unknown. Various theories have been evolved and discussed at great length in the literature. The more prominent of these theories were mentioned in an earlier section of this paper. In the authors opinion the theories leave much to be desired and some of the most convincing evidence for neurotropism (6) is equally good evidence for the other popular view—that some families "inherit" a susceptability for neurologic complications in those members who contract syphilis. The role of trauma has been discussed in scientific meetings as well as in compensation courts with no satisfactory decision reached. It is generally conceded, however, that severe head trauma, excessive alcoholism, or other agents which disturb the physiologic equilibrium of the central nervous system may precipiate paresis in a person suffering from asymptomatic neurosyphilis. In spite of this general belief the evidence upon which it is based is sparse and not altogether convincing. The similarity of the symptoms in paresis and those seen in some of the nutritional disturbances of the brain due to advanced age or secondary to excessive alcoholism offer fertile fields for speculation as to the role deficient oxygen or carbohydrate metalbolism may play and even tempts one to think of the avitaminostic states as possible priming agents which set off the paretic explosion. The influence of racial and climatic factors was discussed by Kraepelin, but this phase of the problem has been neglected and needs further study.

The symptoms and signs of dementia paralytica are best understood if they are considered as, *a.* primary symptoms, that is, symptoms and signs due to organic damage to the brain, and, *b.* secondary symptoms, meaning those symptoms which are determined by the personality and previous experience of the particular patient under observation.

a. The primary symptoms are essentially those of any other organic psychosis. Irritability, a general slowing of

all mental processes, errors in judgment and capricious defects in memory are the most common early signs. Minor behavior disorders, and progressive intellectual defects next appear and if unchecked progress until the patient is a "vegetable" displaying little awareness of or interest in the events transpiring in his environment.

The physical and neurological signs are nonspecific and consist of loss of weight, hypersomnia, increase in appetite, various pains of a lancenating or stabbing character, ataxic gait, pupillary irregularities and inequalities in about 70 per cent of cases with Argyle-Robertson pupils in about 40 per cent of them. There is a general hyperactivity of the deep tendon reflexes and many patients show the pathological thumb and toe signs. The speech is usually slurred, and there is commonly a coarse tremor of the tongue and lips. Writing is frequently tremulous and in more advanced cases words are misspelled and entire phrases omitted.

b. The secondary symptoms are those determined by the individual's previous personality and colored by his previous experience. Thus the amiable, aggressive, outgoing individual tends to become euphoric, elated, overactive and to have many expansive ideas. These ideas are often of great wealth, great power or some combination of powers. For example, one expansive paretic proposed to pave our streets with gold and to have silver curbstones. Another presented a handwritten title to a new car "a 64 cylinder 'Jesus Christ Heart Special'" which he asserted would go so fast that it could jump over oncoming traffic. The suspicious, introversial individual will become sullen, irritable, assaultive and have many paranoid ideas during his paretic episode. The dour, sour, sad faced pessimist will show all the signs, symptoms and suicidal tendencies of a true depression or melancholia during his infection. The farmer plants his crops, the preacher prays and the physician conducts new and wonderful cures during his psychotic episode.

Many of the present day texts and papers continue to classify general paresis into the original Kraepelinian groups (2):

"Demented form; depressed form; expansive form; agitated form."

They then proceed to a discussion of the prognosis

in the various forms with opinions which vary considerably as to those forms showing the best response to therapy. The difficulties are obvious. Such a classification is made on the symptoms the patients show as a result of their previous personality pattern, and while precipitated by the organic episode, give little information as to the severity or extent of brain damage.

In most instances, no attempt is made to evaluate the actual extent of the brain damage present. Kraepelin himself recognized the need for a more satisfactory grouping when he stated "Perhaps a better knowledge of the etiological or the pathological-anatomical relationships of the disease will enable us, under a new point of view, to evolve a more reliable grouping."

Strecker and Ebaugh (16) have made an attempt to divide or classify the dementia paralytic cases according to the severity of involvement. This classification is as follows:

"Group A: The deteriorated group, in which destruction of the central nervous system had proceeded to an advanced degree, with little possibility of retarding the disease process. These patients presented definite findings of mental deterioration on examination.

Group B: An organic reaction with psychosis of a functional coloring. Clinically this group included psychoses similar to the functional disturbances seen in manic excitements, with depressions and other reaction types in addition to the organic symptoms present in general paresis.

Group C: Cases without the signs of deterioration of general paresis in which mental symptoms were frequently transitory and exhibited before any signs of deterioration occurred. This group included delirious reactions and neurological irritative phenomena, as seen in convulsive seizures, aphasic attacks and combinations of meningovascular upsets."

A similar grouping was adapted by the cooperative clinic group (21). In both instances it was found that a rather accurate prognosis could be given according to the classification, thus advanced or "type A" paretics of Strecker and Ebaugh had a uniformly grave prognosis while almost all of the mild or "type C" cases improved or recovered under proper treatment. It is believed that all

studies dealing with the efficiency of various treatment methods should use some such classification as it makes comparison between various studies more feasible.

The serological findings in dementia paralytica are more constant than in the other forms of neurosyphilis. The blood Wassermann will be positive in about 60 per cent of untreated cases. The spinal fluid Wassermann is positive in practically all untreated patients. The colloidal gold curve usually has a first zone rise, the cell count is usually elevated to from 15-100 lymphocytes, the globulin reaction is in most instances positive and the total protein content above normal. A typical spinal fluid serology report would be:

Wassermann Reaction 4-4, with .6 cc, .4 cc, and .2 cc
Gold Curve 5555443210
Globulin +
Total Protein 75
Cell Count 40 lymphocytes

Any history of previous treatment should make one depend less upon the laboratory findings, and in all cases the individual patient must be completely studied and all factors considered before a final diagnostic grouping is made.

Juvenile Paresis is a special form of congenital neurosyphilis, and is undoubtedly the most chronic progressive type of neurosyphilis. The symptoms may appear in infancy or at ages up to the early twenties. Your author is reluctant to make such a diagnosis in adults unless there are other definite signs of congenital syphilis such as malformed teeth, or interstitial keratitis. Previously indiscreet young housewives or careless young men often convince the newly acquired spouse that their syphilis was congenitally acquired, but in most instances the prefix "con" is an affectation prompted by circumstances and the principal portion of the word contains more of the truth. Wm. Menninger has written extensively on this form of neurosyphilis (22 and 23) but most authors tend to neglect it. Some of these patients are intellectually retarded from birth and the diagnosis is often made by the pediatrician or psychiatrist who examines the child because of failure to show the proper intellectual development. In many instances the child may develop normally and show satisfac-

tory progress in his school and social relationships until the age of 8 or 10 years. The parents then notice a progressive dullness, loss of interest in friends, play, possessions, etc. This may be accompanied by a slowing or arrest of physical development, convulsions, keratitis, optic atrophy or other signs of progressive C. N. S. damage. The diagnosis is based on the clinical findings plus the uniformly present paretic formula in the spinal fluid. The blood is also positive in the majority of these children.

In general, the energetic treatment of congenital syphilis is unsatisfactory and cases are reported (24) in which the picture develops in children who have had years of intensive chemotherapy because of a known positive blood in infancy.

b. Tabes Dorsalis:

(Locomotor ataxia) is a syphilitic invasion of the spinal cord, the principal damage occurring in the dorsal columns and the sensory roots. The period between the initial infection and the development of tabes varies from 1-20 years although the average interval probably approximates 15 years. The mode and process of invasion of the cord is not understood as has been stated in an earlier section. The spirochetes are rarely found in or near the tabetis lesion and the changes appear to be due to some accumulation of material about the nerve roots, secondary toxic element, or perhaps to some induced deficiency. Stone (25) reports posterior column lesions resembling tabes in animals fed on diet deficient in Vitamin B complex and Vitamin E. He reports that administration of these preparations had a favorable influence on the response to treatment in humans suffering from tabes dorsalis.

The symptoms and signs are characteristic and may consist of any or many of the following: ataxia, vertigo, diplopia, failing vision, various lancinating and dull aching pains, gastric distress, vomiting attacks, parathesias and numbness, difficulty in performing finely coordinated movements, loss of sex power and decrease in desire, incontinence of bladder often and bowel rarely, girdle pains and failing strength in the legs. The neurological signs are typical and almost always include pupillary anomolies such as unequal, irregular, fixed pupils, or typical Argyle-Robertson pupils, hyperesthesias, diminished tendon re-

flexes, and decreased vibratory and position sense. Many cases also show ataxic gait, cranial nerve palsies, reduced pain sense, optic atrophy, cord bladder, trophic ulcers of the feet, positive Romberg and marked incoordination.

About 30 per cent of cases have a negative blood Wassermann, but a positive spinal fluid reaction (26). In at least 5 per cent of tabetic cases not previously treated for syphilis, the blood and spinal fluid serologies are persistently negative. Thus, one must rely less upon the laboratory and more upon the clinical signs than in the other forms of neurosyphilis. A peculiar arthropathy known as "Charcot joint" sometimes occurs in tabes dorsalis. It consists of a gross serous effusion into a joint, most commonly the knee, which recurrs rapidly after aspiration. The articular cartilages are destroyed and the end of the bone partially absorbed. A large flail joint results which produces odd deformities and great incapacity, but little pain. Trauma seems to precipitate this condition in some patients although in others no traumatic history is discovered. Many authors believe it entirely due to vasomotor changes secondary to the damage to the nervous system.

c. Primary Atrophy of the Optic Nerve.

This syndrome may occur as the only clinical manifestation of neurosyphilis, but it is more often associated with one of the other types of neuroluetic involvement. It is associated with tabes dorsalis more than twice as often as with the other types (27), and is rather rare in clinically pure cases of dementia paralytica. Moore states (27) "Primary optic atrophy was found to occur in at least 8 per cent of all patients with clinical evidence of acquired neurosyphilis." The latent period varies but symptoms most often appear in the second decade of the infection (27). In Moore's series (27) of 250 patients only 1.3 per cent had received adequate treatment for early syphilis. The course varies greatly in untreated patients and Moore (27) gives the following figures:

28 per cent blind within one year of onset
50 per cent blind within two years
65 per cent blind within three years
75 per cent blind within six years
90 per cent blind within twelve years

Thus patients not blind within three years of the onset of symptoms did fairly well, statistically, without treatment. Moore (27) states that "It is probable that the fundamental process is the same in all types of neurosyphilis" and doubts that adhesions about the optic chiasm are contributing factors. The onset is characterized by complaints of "haziness" or "cloudiness" of vision and with a reduction of peripheral vision. The involvement may be unilateral (4 per cent) or bilateral at the onset, but in most instances affects both eyes. Examination reveals a paling of the optic discs and a decrease of the color and then the form fields. The fields for green are usually most seriously involved, but utimately even central vision is lost and total blindness ensues. The prognosis is less favorable if central scotoma is the initial symptom. Treatment may modify the course of the atrophy if instituted early in the course and pursued with judicious energy. The treatability of the type with unilateral onset is often favorable if instituted while only one eye is involved. Primary atrophy is often associated with one of the other types of neurosyphilis and the progress of the generalized infection is not always reflected in the course of the optic atrophy. For example, patients of either the tabetic or tabo-paretic types may become progressively blind during a period in which the tabetic or paretic symptoms are showing a very satisfactory remission.

It must be reemphasized that the above clinical types are not always seen in pure form. The patient usually shows evidence of some involvement of a type other than the major symptom complex. For example, a combination of tabes dorsalis and general paresis known as tabe-paresis is common in any large clinic. Many general paralytics will show episodes of vascular involvement or evidence of meningeal irritation. These combinations are to be expected in that syphilis is a generalized infection and the entire body as well as the entire nervous system is infected and the clinical divisions are made in terms of the area of major involvement and for purposes of organization of the discussion.

PATHOLOGY

a. Asymptomatic Neurosyphilis

Patients rarely die in this phase of the illness and no definite pathology is described.

b. Syphilitic Meningitis.

Death is also rare in this form and the pathological material is correspondingly scanty. In the acute form the pia-arachnoid is opaque and there is a great accumulation of lymphocytes and a few polys in the fluid. In chronic cases the perivascular spaces show an accumulation of round cells. There is also a beginning thickening of the vessel walls due to preliferative changes in the intima and media. There are areas of thickening and adhesions of the pia-arachnoid.

c. Vascular Neurosyphilis, and

d. Diffuse Meningo-vascular Neurosyphilis

In these two forms there is a widespread involvement. The vessel walls show some thickening due to proliferative changes as described above. This may eventually proceed to a thrombosis with resultant ischemic changes in the brain parenchyma. The pia-arachnoid becomes thickened and often adherent to the dura as well as the cortex. Various cranial nerves may be involved in this process which explains some cases of oculomotor palsy and an occasional case of atrophy of the optic nerve.

3. Parenchymatous Neurosyphilis.

1. General Paresis.

The pathological material in this form of neurosyphilis is abundant and well described. Grossly the membranes present a ground glass appearance and adhere to the skull, the brain cortex, and to each other. The brain is diminished in weight and shows diffuse atrophy which is most marked over the frontal lobes, but which is also manifest by the enlarged ventricles.

The microscopic findings are those of any chronic encephalitic process. There is an infiltration of plasma cells and lymphocytes into the membranes, and into the perivascular spaces. This perivascular accumulation of cells produces the well-known "perivascular cuffing" described in all texts. There is a marked increase in the number of small blood vessels, and they appear to run through the tissue in a rather disorderly pattern. The nerve cells are not greatly reduced in number. The usual cortical layers are clearly defined. Many cells are seen in the

process of destruction. Partially degenerated nerve cells covered with glial cells, like currants on a cookie, are common and the picture is described as "neuronaphagia" and often referred to as "coffin formation." There is a marked proliferation of glial cells, and elongated microglia or "rod cells" scattered throughout the cortex is a classic finding in the brain of the paretic patient. Another finding typical of general paresis is the presence of iron pigment in the tissues of the cortex. Untreated cases show many spirochetes in the tissue from the frontal lobes (5).

2. Tabes Dorsalis.

The pathology of tabes is usually described in the late stages and consists of extensive dorsal column degeneration and partial involvement of the sensory roots. This late picture is not typical of the treatable stage of the disease, however, and the following material taken from the lecture notes (Vintage of 1932) of Dr. Stanley Cobb contains an excellent physio-pathologic picture of the changes found in the rare early tabetic material coming to the laboratory.

"Tabes dorsalis (locomotor ataxia) is essentially a symmetrical affection of peripheral afferent neurons. The lesion is a degeneration of the central prolongations of the dorsal root ganglion cells. Just what the mechanism of this degeneration may be has been the subject of much controversy. Strumpel considered the process to be a primary toxic degeneration. Obersteiner considered that it was explained by meningitis nipping the root just as it enters the cord. Marinesco considers the process a primary degeneration of the dorsal root ganglia. Nageotte finds a constant focus of granulation tissue in the minute pocket where the dorsal root pierces the dura, and believes that spirochetes at this point (shown by Richter) cause the selective degeneration. Ingvar explains the selective degeneration of the dorsal columns by the fact that the surface fibres of the dorsal roots are the ones which go to make up the long tracts of the dorsal columns. These are the first destroyed by the chronic syphiletic meningitis. According to Greenfield a composite theory gives the best explanation, and it must be remembered that toxins may have a definitely selective action, in an unknown and apparently arbitrary way destroying some fibres and sparing

others. Spielmeyer accepts this idea and thinks that the syphilitic toxin has a selective effect on the dorsal tracts and sometimes on the optic and auditory nerves just as methyl alcohol picks out the optic nerves and lead often affects only the extensors of the wrists and ankles.

Whatever the exact mechanism, the result is that the dorsal roots first degenerate just within the cord, and the ventral roots are spared. Since all the entering fibres, except those carrying proprioceptive stimuli, have immediate relays of synapses, the conspicuous cord degeneration is in these long proprioceptive fibres of the dorsal columns—the gracile and cuneate tracts. The short fibres also degenerate early but since they plunge quickly into the gray substance to arborize about new cells, they do not cause tract degenerations. The degeneration of those short fibres destined for the dorsal nucleus (of Clarke) may make in Wiegert preparations a small clear area along the edge of the dorsal horn and around the dorsal nucleus. Afferent fibres carrying touch, pain and thermal stimuli may also be affected as is shown by the common segmental skin anesthesias. The typical symptom, however, is ataxia (loss of sense of position) of the legs; with this always goes loss of muscle tone and of tendon reflexes (knee jerks or ankle jerks). The bladder reflexes are also impaired. Pain is a frequent symptom, perhaps due to active root irritation. In the thoracic cord the afferent visceral fibres may be affected, causing the violent pain of "gastric crises." In the late stages, when skin sensation is lost, trophic ulcers of the toes and fingers are found, and painless atrophic joint lesions (Charcot Joints)."

TREATMENT: I. General discussion.

The treatment of neurosyphilis is somewhat different from the treatment of the other forms of a syphilitic infection. Many patients with syphilis never develop symtoms of neurosyphilis (Sec. B) and some fail to show serological evidence of infection of the nervous system by present laboratory and clinical methods. When the infection becomes manifest in the central nervous system, it becomes difficult to treat because of the inaccessibility of the brain, the cord and their coverings, and special treatment methods are required. In the following sections, these special treatment methods will be discussed in some detail. The rou-

tine treatment of syphilis will not be discussed as it is beyond the scope of this paper.

The treatment of neurosyphilis should be primarily prophlyactic. The energetic treatment of all cases of early syphilis would probably prevent the development of neurosyphilis except for a few cases of the parenchymatous type. These may also be prevented when we more thoroughly understand the factors preventing parenchymatous involvement in one case and permitting it in another. Asymptomatic neurosyphilis must be energetically treated by routine methods and when progression continues in spite of such treatment, special therapies should be instituted. In neurosyphilis each case must be studied carefully and the treatment planned according to all the facts, clinical, laboratory and social, in each individual case. Outlines will be presented, but merely as suggestions or guides in planning the therapy in a particular case. Many clinics proceed along conservative lines in the treatment of neurosyphilis. This caution is laudable so long as it is alert conservatism and not a screen for partial inaction or neglect in a particular case. Too many patients come to the neuropsychiatric clinic with far advanced neurosyphilis, many beyond hope of reclaimation, who have been known to have involvement of the nervous system for two or more years, but who have been neglected under the guise of conservative treatment. The following outlines are those used by the author. Many of the ideas represent those culled from the works of Moore, O'Leary, Simpson, Stokes, and the publications of the co-operative clinic groups of the U. S. Public Health Service, and as modified by experience in the management of these patients. I gratefully acknowledge my debt to those authorities and wherein we differ, it is with due respect and with full knowledge of the possibility that I may be overly aggressive in the treatment program, but this attitude has been nurtured by the experience of seeing many previously treatable neurosyphilis patients managed "conservatively" and "observed" until they develop full-blown paretic states.

II. Outline of Therapy and the Various Types of Neurosyphilis.

a. Asymptomatic Neurosyphilis

Authorities differ more widely on the treatment of

this form of neurosyphilis than in any other stage. Most persons agree with Moore (10) "The prognosis of asymptomatic neurosyphilis is equally gloomy whether discovered early or late in the course of infection, unless the development of clinical neurosyphilis is prevented by appropriate intensification or modification of treatment." The difference in management in various clinics lies in the degree and type of "intensification" used. In a distressingly large number of clinics this means merely more neoarsphenamine and less heavy metal. Intensification of routine treatment should mean an increased dosage of arsphenamine. .45-.60 grams given every 4-5 days, and given by the continuous program. Patients with Group I serology may respond to this program. If at the end of 3 to 6 months there is evidence of progression or in the face of failure to improve, tryparsamide and fever therapy should be added to the armamentarium. The plan of treatment used by your author is modified somewhat in terms of our own experience. It will be noted that tryparsamide and fever are used at an earlier stage than that recommended by many authorities. The reason for this is the belief that asymptomatic neurosyphilis is the first stage of invasion of the central nervous system and is "asymptomatic" only because of the limitation of our present methods of clinical observation. The optimum time for the treatment of neurosyphilis is in this stage before irreversible damage occurs.

Outline for Group II Serologies: (See Sec. D,I)

1. 20 injections of tryparsamide of 3 grams each.
2. 6 weekly injections of neoarsphenamine of .6 grams each.
   (Mapharsen .06 grams every 5 days may be substituted.)
3. Recheck of neurological, mental, physical and blood and spinal fluid serological examinations.

If improved

4. Repeat 1.
5. Six weekly injections of bismuth in oil of .26 grams each.
6. Repeat 3.

If the examination at 3 shows progression or no change in the spinal fluid the routine for Group III and

IV is substituted.

Outline for Group III and IV serologies.

1. Fever therapy
   a. Malaria therapy. 50 hours of fever about 104° F. (R.) or
   b. Artificial fever therapy. 36 hours of fever at 105.8° F. (R.)
2. 20 injections of tryparsamide of 3 grams each given at weekly intervals *and* 8 injections of bismuth salicylate of .26 grams each given during the first 8 weeks of tryparsamide therapy.
3. 6 weekly injections of neoarsphenamine of .6 grams each—Mapharsen .06 grams given at 5 day intervals may be substituted.
4. Re-check physical, neurological, mental and complete serology examinations.
5. 20 injections of tryparsamide.
6. 6 injections of bismuth.
7. Repeat 4, 5, etc. for a minimum of 2 years of continuous therapy, or for a minimum of 3 years of treatment in cases who remain serologically positive in spite of continuous treatment.

If at any time there is evidence of clinical progression the fever therapy should be repeated. In our experience with this routine almost all cases respond satisfactorily. Those who fail to do so usually had paretic formulate (Group IV) when first diagnosed and they usually develop clinical signs of tabes dorsalis or general paresis. In these cases, however, the clinical symptoms are usually of the mild type and continued energetic treatment will usually result in a satisfactory remission.

Simpson (28) has had a similar experience with the energetic treatment of patients in this group. He reports that 61% become seronegative when treated with combined fever and chemotherapy and found definite improvement in another 16%. None of his patitnts have shown any clinical signs during the period of observation. Simpson also presents the statistics of Troutman of the U. S. Public Health Service who found serologic reversals in 66% of his cases treated by fever-chemotherapy program and reports no development of clinical signs of neurosyphilis in the observation period of his patients.

b. Meningeal neurosyphilis

Acute syphilitic meningitis respresents a medical emergency and prompt energetic treatment is recommended by all authorities. In many clinics therapy consists of arsphenamine injections of .6 grams each at 3-5 day intervals plus treatment with one of the heavy metals, usually bismuth. In this group we also treat patients aggressively and our routine is as follows:

Treatment Outlined for Acute Syphilitic Meningitis

1. Artificial Fever Therapy.
   12 bi-weekly heatings of 3 hours each at a temperature of 105.8° F (R.).
2. With each heating we administer neoarsphenamine .45 grams (or Mapharsen .04 grams) and bismuth salicylate .26 grams.
3. Recheck of clinical and serologic status.
4. If fluid and clinical status are improved or normal give 12 weekly injections of neoarsphenamine of .6 grams each, then
5. 12 weekly injections of bismuth of .26 grams each.

Complete clinical and serological rechecks should be made each 6 months. The occasional patient who comes to the hospital with a temperature of 105° or over does not receive the artificial fever therapy, but takes the chemotherapy according to the above outline. Fever is always by one of the mechanical devices because the incubation period of malaria is too long to be of benefit in this disorder.

Chronic syphilitic meningitis is treated by the same routine. Fever need not be given as the first stage in treatment and the patient may receive a course of chemotherapy before fever is instituted. In this form therapeutic malaria may be used as well because the course is not so fulminating as in the acute form.

Death rarely occurs in the early phase of either form of meningeal neurosyphilis. Many of the acute cases recover from all symptoms if properly treated, but they should continue for a minimum of 2½-3 years of continuous chemotherapy irrespective of the clinical or serologic improvement. About 30% of improperly treated cases will show progression to a more serious form of neurosyphilis. A few cases will recover from the acute phase, only to later

develop more serious symptoms of the paretic or tabetic type. It is the occurrence of these latter cases that prompts us to use the more radical treatment method of administering fever therapy with the arsenicles in the early stages of the infection. In the chronic form of the disorder, the symptoms due to adhesions and thickenings tend to persist irrespective of the type or quantity of treatment. Energetic treatment in the early phase with prevention of these symptoms as its goal is to be preferred. Surgical relief of the chronic adhesive phenomena has been advocated in these cases showing progressive atrophy of the optic nerve due to adhesions and thickening of the membranes about the chiasm and nerve trunks. This operation will bring about an arrest of the progress of symptoms in some cases. In many instances, however, the adhesions again form and the process goes on after a quiescent period of 6-8 months. It is to be recommended only in those cases where the patient shows a progression of symptoms in spite of intensive treatment, where the diagnosis is definite, and where skilled neurosurgical aid is available.

c. and *d.* Vascular Neurosyphilis and Diffuse Meningovascular Neurosyphilis.

The treatment problems in these two forms of syphilis are essentially the same and they will be presented together. These forms of neurosyphilis offer more difficulties in treatment than the other forms because too much intensification of treatment may result in the patient's death and too little will allow a progression of the disease. One is faced by the unpleasant fact that the vessel walls are involved in the luetic process, that intensive treatment will produce a rapid dissolution of this tissue and that the symptoms due to the vascular lesions may be increased. Treatment is instituted which it is hoped will replace the luetic tissue with scarring and thus prevent vascular accidents of a serious nature.

Treatment Outline for Meningovascular Syphilis.

1. 12 weekly injections of bismuth salicylate of .26 grams each.
2. 12 weekly injections of neoarsphenamine of .45 grams each.
3. Complete clinical and serological recheck.

4. If stationary or improved 20 weekly injections of tryparsamide of 3 grams each.
5. Repeat bismuth, neoarsphenamine, etc.
6. If at end of 6 months there has been no recurrence of the vascular phenomena, and there is evidence of beginning parenchymatous involvement, the fever-chemotherapy routine used in general paresis should be instituted.
7. In cases showing rapid progression with convulsive or vascular phenomena one must plan further treatment according to the individual details of the case. Fever therapy is quite dangerous in patients suffering from repeated vascular accidents. Tryparsamide is to be preferred unless paretic symptoms are progressing so rapidly that the hazards of fever therapy are warranted.

Many individuals with this form of neurosyphilis respond satisfactorily to the more conservative treatment outline above. Convulsive phenomena or residuals of previous hemiplegias may remain as souvenirs of their illness, and they usually show little change irrespective of the treatment routine. The chemotherapy program should continue for a minimum of 2½ to 3 years. Continued therapy is warranted because some of the patients, especially those who originally have "paretic fluids," may show clinical progression, and develop the signs and symptoms of general paresis. With proper management about 80% of these patients give a satisfactory response to treatment. The others usually develop general paresis or become permanent cripples due to major vascular accidents.

E. Parenchymatous Neurosyphilis

a. General Paresis.

In this form of neurosyphilis the preferred plan of treatment is essentially the same in the various clinics throughout the world. Treatment is immediate, intensive, and prolonged. This most feared form of neurosyphilis could probably be prevented in the majority of instances by adequate treatment of early syphilis or by energetic treatment of neurosyphilis in the asymptomatic stage. Some authors believe that a small number of individuals will develop dementia paralytica irrespective of the treatment in the early stage. This concept seems an unreasonable

resignation and should prompt a more vigorous treatment of the early forms of syphilis than our present methods offer.

Treatment Outlined for General Paresis.

1. Fever therapy
   a. Malaria therapy
   50 hours of fever at a temperature above 104° F (R)
   or
   b. Artificial Fever therapy
   12 heatings of 3 hours each at a temperature of 105.8°F (R), given twice weekly. Chemotherapy is given with each heating.
2. Tryparsamide. 20 weekly injections of 3 grams each, combined with
3. 12 weekly injections of bismuth salicylate given during the first 12 weeks of tryparsamide therapy.
4. Then give 12 weekly injections of neoarsphenamide of .45 grams each. (Mapharsen .04 grams every 5 days may be substituted.)
5. Repeat 2, 3, and 4, by continuous plan for a minimum of 3 years.
6. Complete clinical and serological check each 6 months.
7. Patients should remain under observation during the remainder of their life with annual check-ups of clinical and serogolic findings.

The technical details of administering fever therapy, the relative merits of the various methods of inducing fever and the complications to be avoided will be discussed in a latter section. The special precautions necessary when using tryparsamide will also be presented at a latter time. The literature since the early 1920's contains hundreds of reports concerning the results to be expected in the use of the various types of fever therapy and chemotherapy in the treatment of paresis. It would be impossible to present all of these and only a few will be mentioned. Solomon and various co-workers (29) (30) (31) (32) have written extensively on the treatment of this form of neurosyphilis. They have done statistical studies comparing the efficiency of tryparsamide alone and chemotherapy with malaria therapy in the treatment of this disorder.

They have also done some work with the use of diathermy and chemotherapy in the treatment of paresis, but in this latter phase of the problem their results are at variance with most other workers in the field. O'Leary (33 and 34) has written extensively in this field, and his work will be referred to in a later section. Wagner Jauregg, the founder of the modern treatment of neurosyphilis has written numerous papers on this disorder and his results are well known. A summary of his experiences (35) was published in 1939 and after a very thorough and fair discussion of the various treatment methods he concludes "The best treatment of progressive paralysis still remains prophylactic; that is, the energetic treatment of latently positive spinal fluid if found by investigation of the fluid between the 3rd and 15th year after infection. The greatest safety requires an energetic treatment by chemotherapy instituted immediately after infection so that the lodging of the spirochete in the central nervous system will in general be minimized." Brown (36) has reviewed the literature on over 5000 cases of paresis, approximately half of which were treated with malaria and the others untreated. The remission rate in the untreated group is reported as 4.3%, and in the malaria treated group the remission rate was found to be 53%. The section of his papers dealing with heliotherapy for paresis is not recommended. As previously stated there are a number of other papers in the literature. Some of these claiming spectacular results by the use of oral bismuth or oral preparations of various arsenical compounds present interesting data for speculation, but unfortunately the reports are not verified by later workers in the field and such methods are therefore not recommended. The best statistical study available is that of the Cooperative Clinic Group of the Public Health Service headed by O'Leary (21). Their results are of great importance and are presented in some detail from their report, "Clinical Results."

"1. Under either method of fever therapy, the earlier in its course the paresis was treated the more favorable were the results of therapy.

2. The chances of clinical remission in patients with mild paresis were approximately one out of two; interme-

diate paresis, one out of four, and severe paresis, from one to ten out of one hundred.

3. Clinical responses to either type of fever therapy were similar in patients with mild or intermediate paresis on beginning fever therapy. However, this similarity disappeared when treatment was administered to patients with severe paresis. In fact, the remission rates for patients with severe paresis treated and observed for the same length of time was one out of 100 with malaria, as compared with ten out of 100 with artificial fever.

4. Treatment deaths were defined as due to treatment regardless of cause, provided death occurred within three months of the fever therapy. Under this definition the crude death rate was higher with malaria (13 per cent) than with artificial fever (8 per cent). The more severe the paresis on beginning treatment with either type of thrapy, the higher was the frequency of death. Within each degree of paretic involvement the crude death rate was higher under malaria than under artificial fever. These differences in death rates by degree of involvement under the two methods of fever therapy were not statistically significant but as a series they all point in the same direction.

5. Approximately 90 per cent of the total clinical remissions obtained under either method of therapy occurred by the end of the third year of treatment-observation. The degree of paretic involvement on beginning fever therapy influenecd the frequncy and the speed of expected remissions. Clinical remissions were obtained from one to two years earlier in patients with mild than in intermediate or severe paresis.

6. None of the patients in whom clinical improvement was delayed until the 3rd year after beginning fever therapy at any time reached the remission stage. Of 432 patients with clinical improvement during the first or second years after beginning fever therapy, 34 per cent of those with clinical improvement the first year and 12 per cent of those in whom clinical improvement was delayed until the second year subsequently achieved complete clinical remission.

7. Once a complete remission had been obtained, the chances of its being maintained under either method of fever therapy were 95 out of 100. In a total of 17 relapses, 15 occurred within 3 years subsequent to the year

of remission. Relapses were more frequent in severe paresis than in mild or intermediate paresis.

Serologic Results

1. Reversal rates for original positive spinal fluid and blood increased as the duration of treatment-observation increased.

2. Positive blood reversed more rapidly though not in greater proportion than positive spinal fluid. The degree of spinal fluid abnormality on beginning fever therapy influenced the proportion of expected reversals.

3. In patients treated with fever plus chemotherapy the annual rates of spinal fluid as well as blood reversal were consistenly higher with malaria than with artificial fever, but this difference was assumed to be due to the greater amount of chemotherapy (17 per cent more) administered to the malaria patients. Without the use of auxiliary chemotherapy there were no differences between the spinal fluid and blood reversal rates of patients treated with malaria and those treated with artificial fever.

4. Blood as well as spinal fluid reversal rates were at least twice as great with as without the use of auxiliary chemotherapy. Among patients not treated with auxiliary chemotherapy 42 per cent of all spinal fluid reversals subseuently relapsed as contrasted to only 24 per cent spinal fluid relapses among patients treated with auxiliary chemotherapy.

5. Two thirds of all the relapses from spinal fluid reversal occurred within one year following the original reversal.

6. Negative blood serologic reaction did not indicate the status of the spinal fluid, but persistently positive blood serologic reaction was indicative of positive spinal fluid reaction.

Relation of Clinical to Serologic Results

1. Reversal of both blood and spinal fluid were associated more than twice as frequently with clinical success as with clinical failure. However, since clinic success was not accompanied by completed reversal (blood and spinal fluid) in 52 per cent of the cases it follows that clinical success was not necessarily dependent on serologic reversal.

2. Reversal of the spinal fluid was more important than reversal of the blood in indicating the chances of complete clinical recovery.

3. In three-fourths of the cases with clinical as well as serologic recoveries the clinical remission proceeded or occurred during the same year as the serologic reversal. When the clinical remission proceeded the serologic reversal, it did so by an average difference of from 2 to 3 years. In the remaining fourth of the cases in which serologic recovery occurred first an average of from 2 to 3 years elapsed before clinical remission was obtained."

Our own experiences with the treatment of general paresis has been summarized (37) and we have found that between 60 and 70% of patients suffering from general paresis are benefited by combined intensive fever chemotherapy routine. It is our feeling that the statistical difference recorded in the cases from various clinics depends upon the type of case treated, that is, the proportion of mild and deteriorated cases, and the efficiency of the follow-up chemotherapy program. It is interesting to note that the originators of modern fever therapy both brought about these methods in a search for a more satisfactory treatment of neurosyphilis. Wagner-Jauregg used malaria after finding that tuberculin injections were unsatisfactory and Neymann (38 and 39) originated the first artificial fever method because of his dissatisfaction with therapeutic malaria.

b. Tabes Dorsalis

The treatment of tabes dorsalis should in my opinion be planned according to the guiding principal used in dementia paralytica. That is, intensive, continuous, and prolonged. More conservative clinics treat tabes by the use of intensive chemotherapy alone. In our hands this has resulted in too great an incidence of progression and as a result we use the same treatment outlined as was suggested above for use in general paresis. It has been suggested that the use of fever therapy in tabetic patients showing complications of atrophy of the optic nerve may bring about a sudden total blindness. We have not experienced such disaster and would hesitate to ascribe them to the fever therapy inasmuch as fever therapy has been advocated as the most effective treatment for primary atrophy of the

optic nerve. The Cooperative Clinic Group (40) have reported the results of the treatment of tabes dorsalis. It was shown that 15% were improved following routine chemotherapy, but 26% were improved if tryparsamide were added to the routine. 20% were improved if malaria therapy were used and 25% were improved by Swift-Ellis routine. The desirability of treating tabes by the more aggressive method early in the infection has been emphasized by Simpson (28). "It is unfortunate that the use of fever therapy is still to often regarded as a final resort method of treatment. Much better results will be achieved when it is more generally recognized that fever therapy combined with chemotherapy is the primary treatment of choice in all types of symptomatic and asymptomatic. This fact is particularly apparent in the management of patients with tabes dorsalis."

Our own experience is that early energetic treatment prevents the development of many of the distressing late symptoms. The most distressing symptoms in this disorder are the lightning pains and the gastric crises. We have found that both of these symptoms are often relieved if the patient appears for treatment during the phase in which he has a positive spinal fluid. However, if the symptoms persist in spite of spinal fluid reversal or if the symptoms appear in the seronegative or so-called "burned-out" case the most vigorous chemo and fever therapy have little influence upon the symptoms. In the acute phase the crises are relieved or at least ameliorated by narcotics, but there is the danger of medically induced addiction. We have found it better practice to hospitalize the patient to supply fluids and salt by vein and to give them rest with rectally administered paraldehyde in large doses. The lightning pains usually prove more resistant but these too are best handled by hospitalization and the use of one large dose of some quick acting hypnotic such as paralydehyde rather than piddling administrations of morphine with its inherent dangers of habit formation. Following the period of symptomatic relief we have had some excellent results in obtaining more prolonged relief by deep x-ray therapy over the lower dorsal and upper lumbar spine. The exposure is as follows: Three treatments at 2 day intervals. 300 Roentgens per treatment. Give over 10 x 20 portal over

lower cord region. Depending upon response may treat upper cord. Give at 200 K. V. ½ copper plus one aluminum filter.

In a small series of case we have had excellent prolonged relief from both crises and pain and to date have had no complications from over radiation. This technique is one requiring considerable finesse and should always be administered by a roentgenologist who is experienced in administering deep x-ray therapy. The Swift-Ellis treatment has been advocated, but we have not recently used it in our clinic because of the good results obtained from the above outlined methods of treatment. The Swift-Ellis technique will not be described here because it is a well-known method and is thoroughly described by Moore (10) as well as by other writers in the field.

c. Primary atrophy of the optic nerve is the most difficult form of neurosyphilis to treat and usually results in blindness unless treatment is vigorous and early. Moore (10) states, "Only two forms of treatment seem to be of any avail, subdural or fever therapy; and one of these should be adopted as soon as the diagnosis is made. Any other therapeutic efforts are usually useless in arresting visual failure and constitute dangerous temporizing." In a latter study (27) he advises against the use of subdural therapy. Fever therapy has been recommended by numerous authors. Clarke (41) and (42) has found malaria therapy to be of benefit in this condition. His explanation for the curative action of malaria is probably not all together sound but at least his results are in keeping with those of other workers of the field. Moore and his co-workers have long advocated the use of fever therapy as well as subdural therapy. He has written extensively on the topic (10-27-43) and his most recent article (27) is an excellent treatise on the subject. He reviews 250 cases and finds that if untreated 28% of them become blind in one year after the onset of symptoms and 75% within 6 years. He has found that routine treatment neither hastens nor delays the course, of the infection. Subdural treatment or so-called Swift-Ellis treatment helps in some cases, but about 10% of those so treated may go blind suddenly. Moore found fever therapy, given by means of malaria, to be the best form of treatment, and added 57% to the expected num-

ber of patients with vision at the end of 10 years of observation. In the malaria group only 9% were blind one year after onset and only 18%, 3 years after onset. No other patients lost their vision after the third year during the 15 years of observation. These results contrast with those in the untreated cases in which 28% were blind in one year, 65% in 3 years and 90% in 12 years. These figures are different than those published by Moore earlier (43) but probably represent a more accurate statistical study of a larger group of cases. He feels that intensive chemotherapy should be used in the follow-up treatment, but cautions against the use of tryparsamide. Reese (44) recommended tryparsamide in those cases showing a proportional decrease in visual acuity and color vision. In our own experience fever therapy has been the most satisfactory form of treatment. When the diagnosis is first made, patients are placed on the following routine.

1. Fever therapy of the artificial type, 12 treatments of 3 hours each at a temperature of 105.8° F (R) + neoarsphenamine, .3 grams (Mapharsen .03 grams may be substitnted), and bismuth salicylate, .26 grams with each heating. Treatments are given twice weekly.
2. Chemotherpay consisting of alternating courses of neoarsphenamine and bismuth for a minimum of 2 years.
3. If patients fail to improve after their fever therapy or if the process continues in spite of fever therapy some type of subdural treatment is used. Moore originally recommended the use of arsphenaminized serum starting with a dose of 5 c.c. and increasing to 15 c.c. introduced intracisternally. He recommended one treatment every 2 weeks and administered for a total of not more than six times. Moore recommended the introductions of the serum intracisternally, following the instillation the patient should be placed on his face in order that the heavier arsphenaminized serum may gravitate downward and exert its greatest effect about the optic nerve. About 5 c.c. of spinal fluid in excess of the amount of serum to be introduced should first be withdrawn. In his most recent publication

he cautions against subdural treatment in these cases. We have used Giffords (45) modification of this technique with some success. Intracisternal fluid is withdrawn and .06 c.c. of 1 to 200 white bi-chloride of mercury is added to approximately 10 c.c. of spinal fluid and after gentle agitation the mixture is immediately reintroduced and the patient placed on his face. This treatment has been less successful than the use of fever therapy, but in a few instances has given rather spectacular results and I believe that one of the subdural methods is indicated in patients who fail to respond to one of the forms of fever therapy. It has not been used and should not be used in patients who retain any vision but may be of use in cases who have recently lost their vision.

Hausman (46) discusses adhesive arachnoiditis and offers signs differentiating it from primary atrophy. We have not been successful in making such differentiations but as mentioned under meningo-vascular syphilis, surgical intervention may be warranted in the proper case. Moore (27) doubts the existence of such an entity but others report such adhesions. It is our belief that these patients should be treated first with fever therapy before resorting to surgery because in our experience the fever has been more generally productive of good results. Without treatment most patients become progressively blind. Simpson (28) reports that 25 cases treated in his clinic by an intensive combined chemo-fever therapy routine have remained stationary and none of them have shown any progression of atrophy. Similar reports on smaller groups have been made by Bennett and other workers who are using the same routine. In our experience fever therapy administered early in the course of atrophy has been definitely beneficial. No statistics are available at this time, but the majority of these earlier cases are benefited. In a few instances, however, progression has continued and we have resorted to subdural treatment. Most of the cases failing to respond to fever therapy also fail on subdural treatment although there are a few notable exceptions and because the treatment is relatively safe if properly administered I believe subdural therapy warranted in those

cases who continue on to blindness in spite of fever therapy.

III. Discussion of Tryparasmide

Tryparsamide therapy has a well established place in the management of neurosyphilis and is particularly useful in the treatment of general paresis and tabes dorsalis. Because of certain complications which may produce blindness its use will be discussed in some detail. Tryparsamide was developed by Jacobs and Heidelberger (4) and was first synthesized as a treatment for trypanosomasis. Early workers with the drug found that it readily passed into the nervous system. Lorenz and his co-workers were the first to use tryparsamide in the treatment of neurosyphilis and the present status of tryparsamide therapy has been admirably reviewed by Hinrickson (47).

The principal complication encountered in tryparsamide therapy is its toxic action upon the optic nerve. In neurosyphilis, particularly of the tabetic and paretic type the question of whether the visual disturbances encountered are due to the tryparsamide or due to the development of a primary atrophy of the optic nerve is important. Reese (44) has attempted to make this differentiation, because patients showing atrophy due to syphilis would be benefited by a continuation of the tryparsamide and would be unnecessarily penalized if the treatment were withdrawn on the basis that the blindness was due to the drug. Woods and Moore have made a similar attempt to so distinguish and these authors originally report differences in the field changes produced by tryparsamide and primary atrophy. Reese felt that atrophy due to the tryparsamide produced disproportional changes in the color and form field. In 1924 Woods and Moore made a study in which they felt that in the patients who developed a reaction to tryparsamide, the temporal fields were relatively well preserved as compared to the nasal fields. In reviewing a series of primary atrophies who received no tryparsamide, they did not observe this preservation of the temporal fields in any case. In his more recent works Moore makes no mention of this distinguishing feature. Your speaker knows of no reliable and definite means of distinguishing between atrophy of the optic nerve due to tryparsamide and that due to syphilis, and as a general principal tryparsamide therapy is discontinued in any pa-

tient displaying a visual disturbance. It has also been stated in the literature that 80% of the visual reactions due to tryparsamide occurred between the 1st and 10th doses of the drug. It has also been our experience that the majority of patients who react badly to tryparsamide do so during the first five injections. An exceptional case will develop what appears to be a tryparsamide reaction after 50 or more injections. As I have stated above we cannot clearly distinguish between primary atrophy and atrophy due to tryparsamide. The other toxic effects of tryparsamide therapy are infrequent. The most severe one is jaundice. Occasionally patients will develop a rather typical arsenical dermatitis and on a few occasions we have seen a typical attack of urticaria following tryparsamide injections. We have continued use of the drug in patients having simple urticaria as the only complication and have encountered no further difficulties. Kemp (48) has reported similar cases. In one case the urticaria developed after the patient had been on tryparsamide therapy for many months. The precautions to be used in tryparsamide treatment may be outlined as follows:

1. Careful measurement of the visual field and visual acuity with fundiscopic examination prior to tryparsamide therapy.
2. Check these examinations each 6 months routinely and at any other time that the patient makes any complaint referable to his vision.
3. The subjective symptoms to be watched for are complaints of "shimmering" vision or "heat waves" in front of the eyes. Some patients complain of floating objects similar to those sensations encountered after prolonged exposure to bright sunlight. The symptoms are usually transitory and will disappear within a few days if treatment is discontinued.
4. Objective signs at this stage usually reveal no change although some authors report mild hyperemia of the disc.
5. The next phase is failing or diminution of vision which is present both on subjective complaint and objective examination. Opthalmoscopic examination at this time usually reveals no gross pathology. Vis-

ual fields taken at this time will usually show marked contracture.

If tryparsamide therapy is discontinued at this phase, central vision is almost always preserved and the patient is not seriously handicapped by his reaction, in fact most of them are not aware of the field contracture. It is our policy to administer sodium thiosulphate at this time, but I am skeptical of its value. If the symptoms are overlooked, blindness may come either suddenly or by slow progression. The latter is the more common course. One will occasionally see an atrophy developed within a period of one to two days which progresses to total blindness in this short period. We have attempted to treat two such cases with fever therapy and with subdural therapy, but with a remarkable lack of success. In our rather extensive experience with tryparsamide therapy those are the only two cases of atrophy apparently due to tryparsamide who failed to give adequate warning by the symptoms mentioned above. It is our policy to watch patients closely and to discontinue the use of tryparsamide upon the development of any definite objective changes. At the first subjective complaint, therapy is discontinued until the subjective findings can be checked, but it may be resumed cautiously with frequent re-examination if the objective findings should prove unchanged from the pre-treatment level. In patients with advanced general paresis where the drug was especially indicated, we have cautiously resumed tryparsamide therapy in the face of definite objective changes in the fields. This is not recommended and should be reserved for those persons experienced in the use of the drug and then used only in patients where tryparsamide is thought to be the difference between an improvment and progress of the disease in advanced general paretics.

A new pentavalent arsenical called "aldarsone" has been tested (49 and 50) and the preliminary reports are encouraging. If further experience confirms the early reports of low toxicity and high therapeutic value it will be a valuable addition to our chemotherapeutic armamentarium.

IV. Fever Therapy

a. Therapeutic malaria

Therapeutic malaria has been used more extensively than any other form of fever therapy. It was discovered

by Wagner-Jauregg and its present method of application was perfected by him. His work with malaria has been summarized in his obituary written by Bruetsch (51). Wagner-Jauregg himself summarized his feelings concerning the management of paresis in 1939 (35). The literature contains innumerable reports concerning the efficiency of malaria therapy and some of these have been previously referred to in the section on treatment. Some authors (52) (53) have postualted that malaria therapy works by a stimulation of the reticulo-endothelial system. Davidson (52) postulates that the leucopenia brings about this stimulation. Bruetsch who has written most extensively on the topic believes that the capillary endethelium preliferates as part of the reticulo endethelial reaction and that malaria specifically brings about this stimulation. Some workers, notably Bruetsch, feel that malaria therpay may be effective even though it produces no febrile paroxysms and they feel that the reaction is due to some specific action of the malaria itself. Needles (54) has shown that patients with endemic malaria have a very low incidence of neurosyphilis. This is an observation similar to that originally made by Wagner-Jauregg prior to his development of malaria therapy. Beck (55) conducted a series of experiments in which he attempted to show the presence of specific immune bodies in malaria sera which would reduce the susceptibility to syphilis. He was unable to detect any difference between the action of malaria sera and the serum from normal animals. The Cooperative Clinic Study (21) shows a definite correlation between the height of fever and the therapeutic results irrespective of the method of heating used. It is therefore improbable that the malaria plasmodium per se has any direct therapeutic action, but the beneficial effects seem to be due to the febrile response and the various temporary physiologic changes produced by the fever.

Patients should have careful clinical and laboratory examination prior to inoculation with the malaria plasmodia. Advanced age, marked hypertension, pulmonary tuberculosis, marked anemia, renal insufficiency and cardiac insufficiency from any cause, make malaria therapy a hazardous procedure and are ordinarily considered to be contraindications. Each case must be considered individ-

ually, however, and treatment planned according to the patient's particular needs. The technique of therapeutic malaria has been described in some detail (56), but a brief discussion of the technique will be included in this paper.

The parasite most commonly used is the Plasmodium Vivax or so-called "tertian malaria," which in pure strain produces a chill and fever each 48 hours. Certain patients are resistant to "tertian malaria," particularly Southern negroes, and in these cases "quartian malaria" from the Plasmodium malaria will often infect the patient. Branche (57) has used it extensively and finds it to be equally effective to the tertian form. He believes the 72 hours interval between paroxysms to be of advantage because it allows the patient more time to recuperate between bouts. The disadvantage of this form is the fact that the incubation period is long and thus holds patients in or near the hospital longer than is desirable from an economic viewpoint.

Instructions for Therapeutic Malaria

1. Check blood count, blood type; blood chemistry for N.P.N., urea, creatinine, and sugar; urine; and skin for quinine sensativity. Take E.K.G., chest x-ray and visual fields.
2. Inoculate patient with 2 cc of blood intravenously or 6 cc of blood intramuscularly taken from another patient who is running a course of malaria. If the donor is in another ward of different city, the blood should be citrated upon withdrawal and placed in a sterile test tube. It may be kept for 2-4 days at room temperature and sent in ordinary mailing cartons to any part of the country by air mail.
3. During the incubation period, and before inoculation, patient should be on high caloric, high vitamin diet. Iron preparations are given routinely to help prevent and combat anemia.
4. With the intial chill patient should be covered with blankets and hot water bottles to encourage the temperature rise.
5. Blankets and bottles should be left in place after the chill in spite of patients protests as it will maintain a high fever level for a longer period of time. During this period patient may drink tap water, but it should not be iced.

6. Temperature should be checked each 10 minutes during the rise and each 15 minutes thereafter. Temperatures of 105-106° F (R) are well tolerated by most patients. Temperature may be maintained for 5-6 hours at a level of above 104° F (R), but in most instances it will fall spontaneously before this time elapses.
7. Quinine and antipyretic drugs should not be administered.
8. If the temperature goes above 106° F (R) or persists beyond 6 hours it can be reduced promptly by administering 100 cc of 2% sodium chloride I.V. and by allowing an electric fan to blow over the exposed body while a nurse rubs it vigorously with bathing alcohol to bring flushing of the skin.
9. Blood pressure is checked daily, urine twice weekly and blood N.P.N. and urea weekly.
10. Betwen bouts patients receive fluids in abundance and 45 grains of sodium chloride daily.
11. After 50 hours of fever above 104° the malaria may be terminated. In institutional work make sure that transfer of the plasmodia to the next patient is carried out before termination is started. Then order quinine sulphate grains X T.T.D. for 10 days and grains XX one day each week thereafter for 6-8 weeks. At the same time start neoarsphenamine .3 grams increasing to .6 grams for 4 doses. Patients are then started on tryparsamide as outlined under general paresis. Complications are infrequent and usually trivial in properly selected and managed cases.

Secondary anemia may become severe, but is avoided in many cases by the routine use of one of the iron preparations in large doses, i. e., iron and amonium citrate 60 grains daily or Blauds mass 30 grains daily or Fesol 15 grains daily. If the anemia is persistent, transfusion usually boosts the blood count to a satisfactory level. In an occasional case the count will continue to fall in spite of these measures, and may fall below 2 million r.b.c. In such a circumstance the treatment should be terminated but this does not contraindicate re-inoculations at a later date after the patient regains a normal count.

Leucopenia is a physiologic concomitant of malaria and must be expected. Micro-movies have shown that the leucopenia is probably due to an adherence of the leucocytes to the walls of the smaller arterioles, and to a clumping of the blood cells. It is probably unnecessary to terminate the infection because of marked leucopenia although some workers believe that a w.b.c. below 2000 cells per cmm. is an indication for termination.

Signs of renal insufficiency such as marked albuminuria, hematuria, casts in the urine, or accumulation of total N.P.N., urea or creatinine in the blood are indications for termination. Mild albuminuria or an occasional cast are danger signals, but the course may be continued with more frequent checks of renal function.

Shock or cardiac failure are infrequent. A low systolic blood pressure with an increased pulse pressure is often encountered and while of no great consequence may be readily combatted by intravenous, saline solution.

Prolonged high fever (106 or over) is a sign of heat stroke and responds readily to fluids and chlorides. The temperature may be brought down quickly as outlined above. The course of malaria may be continued after such an episode, and auxiliary fluids by vein, or under the skin between paroxysms usually prevents the recurrence of this particular complication.

Convulsions may occur, especially in patients with chronic meningeal involvement. They are best combated by hypertonic fluids I.V. and by anti-convulsants such as phenobarbital. In patients with this complication the malaria may be continued cautiously and seizures minimized by daily dosing with phenobarbital gr. 1½ T.I.D., similar to the plan used in epilepsy. If the seizures increase in severity and frequency the malaria should be terminated.

Rupture of the spleen has been described. The majority of these patients show some enlargement and tenderness of the spleen, but we have never encountered this complication. If the spleen seems to become acutely tender or to be greatly enlarged the course of the malaria should be interrupted. In case of rupture, the symptoms would be those of massive intra-abdominal hemorrhage with severe shock. Treatment is transfusion and immediate op-

eration. Patients with neurosyphilis plus malaria do not make good operative risks and they will probably die if this emergency arises.

Intracranial hemorrhage may occasionally complicate the picture. The malaria should be terminated and the patient treated conservatively according to the routine for apoplexy from any cause.

The results from malaria therapy vary in the clinics reporting. This variation is probably due to the degree of involvement of the cases reported, the technique of the persons administering the fever, and the amount and type of follow-up treatment and care.

The Cooperative Clinical Group (21) findings in the treatment of paresis were given above. In our series 58% of the paretic patients were benefited by malaria therapy (37).

Therapeutic malaria is a more hazardous treatment (21) (37) than artificial fever. It is cheaper and simpler to administer to *institutional paretics*. It requires no special equipment and the number of patients treated is limited only by the bed space available and the nursing help at hand. Thompson (58) has advocated home treatment with therapeutic malaria but I could not recommend this method as these patients are very ill and require constant supervision by trained nurses and a physician. Hoch (59) and co-workers recommend the inoculation of a standard number of parasites as a means of producing more uniform incubation periods and a more uniform response to the inoculation. This work is scientifically interesting, but of little practical significance. Malaria therapy thus remains a useful therapeutic weapon in the treatment of neurosyphilis.

b. Artificial Fever Therapy

This term is used to describe fever produced by some physical modality usually called a fever cabinet or "hot box." Temperatures may be induced by hot baths, packing in heated blankets and similar crude devices which have been discussed elsewhere (56). For all practical purposes, however, the physical devices to safely produce fevers are of the "fever cabinet" type.

It is undoubtedly true that the Greeks, the Romans, Japanese and assorted Central American tribes used vari-

ous types of steam baths, hot baths, etc. It is equally true that this was not fever therapy per se and the temperatures produced were probably "piddling" and short at best. Modern artificial fever therapy was originated by Neymann and Osborne of Chicago. The history of this movement, in their hands, has been well presented by Neymann (39) and will not be repeated here. It is interesting to note however, that they developed artificial fever therapy in search for a better method for the treatment of neurosyphilis, because of their dissatisfaction with therapeutic malaria.

Simpson and Kendall, of the Kettering Institute for Medical Research, have also contributed much to the development of the apparatus, the standardization of technique and to our scientific knowledge in this field. Simpson and Kettering inaugurated a nation-wide cooperative research program which has done much to place artificial fever therapy on a sound basis, founded on careful clinical physiologic, and chemical researches carried on with their encouragement and the subsidy of Mr. Kettering.

Simpson has summarized much of this experience (28) as it applies to the treatment of syphilis, and many of the other studies have been compiled and published as a collaborative study, and edited by Simpson and Bierman (60). A further review of the splendid work done in the development of this technique is beyond the scope of this course and those interested are referred to the abundant literature on the subject.

Before proceeding to a discussion of the technique, I should like to mention briefly the matter of the types of fever machines now on the market. This is necessary because energetic salesmen extole the virtues of one machine over the other, blandly assuring you that certain wave lengths or lack of them possess mysterious therapeutic powers. This is, of course, motivated by their own enthusiasm and the desire to make a living. Several machines are satisfactory and any council accepted machine will give satisfactory service.

Apparatus for administering artificial fever therapy is of 3 types. (1) The "short wave" type. This type of machine raises the patient's temperature by the passage

of induced high frequency currents through the body. The temperature thus induced is maintained by means of an air condition cabinet in the more modern machines and by means of an insulated sleeping bag in the older forms. The cabinet models are recommended because the patient is more comfortable and it is easier to check blood pressure, administer parenteral fluids and check the condition of the skin. The operation of this type of machine is discussed in detail elsewhere (56).

(2) Warren and his co-workers favor a type of machine which depends upon radiant energy derived from carbon filament lamps for fever production. This machine utilizes an insulated cabinet to preserve the temperature thus induced. The air in this cabinet is not circulated and the patient's own perspiration supplies enough humidity to maintain a very satisfactory temperature curve. The detailed instructions for the operation of this cabinet are available in the literature (56).

(3) The Hypertherm, or "Kettering Hypertherm" or air condition cabinet is another widely used form of fever producing device. It consists of an insulated cabinet through which hot moist air circulates and the induction of the fever and the maintenances of the temperature is very satisfactory. This is the type of equipment used by the author and it has been very satisfactory in long hard service.

The details of the operation of this type of equipment is also described elsewhere (56) and will not be repeated at this time.

Any hospital planning on the installation of a fever department should have the nurse, technician and a physician visit some training center for instruction in the operation and management of the type of machine to be used. The general management of patients under artificial treatment is the same irrespective of the type of equipment used.

Instructions for Artificial Fever Therapy:

1. Complete check-up including blood chemistry, urine, blood examination, E.K.G., x-ray of heart and lungs, and visual fields.
2. Omit breakfast the morning of treatment. Enema morning before treatment.

3. Temperature is elevated to 105.8° F (R) in 50-70 minutes and maintained for three hours. Patients weak, or in poor general condition, may be treated at temperatures the patient will tolerate. For example, patients of advanced age will often tolerate artificially induced temperatures of 104°. If patient's condition becomes poor, the fever can be reduced at any time.
4. Patients are given abundant salt and fluids during the heating. In our department we routinely administer 2000 cc. Ringer's Solution I.V.
5. Chemotherpay may be administered during or just prior to the induction of the fever.
6. Treatment is terminated by removal from cabinet and cooling with fans.
7. A "course" of treatment in neurosyphilis ordinarily consists of 36 hours of fever at 105.8° F (R). This amount may be increased or decreased as indicated.
8. After the treatment the patient is to remain in bed for 2 hours. May have food and fluids as he desires.
9. Patients may go home 2 hours after treatment unless the status of their neurosyphilis makes custodial care necessary.

Complications are infrequent if the material is properly selected and the treatments skillfully administered.

Restlessness and air hunger during the induction phase is rather common and is promptly relieved by oxygen inhalation for a few moments. If persistent, a Boothby nasal mask is a convenient method of administering the oxygen.

A mild tetany occurs in an occasional patient during the induction phase and is promptly relieved by injection of calcium gluconate intravenously.

Signs of collapse, heat stroke and circulatory failure rarely occur if patients are given adequate fluid and chlorides during the treatment. When they do occur the treatment should be terminated and a venoclysis started, containing hypertonic sugar solution to which salt has been added. Uncontrolled fever is the principal sign of heat stroke and is brought under control by supplying salt and fluids to the blood stream, and by cooling the patient by means of a fan. Alcohol or tepid water sponging, accom-

panied by rubbing to keep the cutaneous vessels dilated and allows the skin to function as a radiator of maximum efficiency.

Debilitated, anemic, mildly sclerotic and diabetic patients may be treated with caution if the clinical circumstances warrant the added risk. Treatment of this class of patients should not be attempted until the department personnel has had considerable experience with the method.

Active pulmonary tuberculosis, advanced arteriosclerosis or advanced syphilitic aortitis are the principal contraindications to artificial fever therapy. We have treated a number of arrested cases of tuberculosis with no reactivation.

In skilled hands artificial fever therapy carries a lower mortality rate than malaria therapy when used in the treatment of neurosyphilis, (21 and 37).

In our experience it also produces somewhat better results than therapeutic malaria, (37). This experience has been verified by other workers (21, 28, 38, 39, and 61), and in my opinion has become the treatment of choice in the management of those cases of syphilis of the nervous system in which fever therapy is indicated. The principal objections to its use are the necessity for trained personnel, and the cost of the equipment.

In our experience the money saved on hospitalization alone more than balances the expense of operating the department. In addition, many working people are able to continue at work, taking treatment on their day off and thus are able to support their families and pay something toward their treatment during the actual treatment period. This is in sharp contrast to the man who must leave his work and his family and be hospitalized during the course of malaria treatment. The patients who require hospital care because of their psychotic behavior or very poor physical condition will require only 6-8 weeks in the hospital. This period is no longer than that required by the case running therapeutic malaria and is much shorter than the period of confinement necessary if the incubation period of the malaria proves to be prolonged.

Hospitals such as state or federal custodial institutions who have the problem of treating large numbers of paretics

who are necessarily institutionalized will find malaria the cheaper form of therapy.

Stafford Warren and his associates at the University of Rochester are experimenting with single, long heatings in the treatment of general paresis. The report of the Co-operative Group (21) would indicate that the height and duration of the fever are the therapeutically important features in any non-specific treatment used in general paresis.

In conclusion, it should be restated that neurosyphilis is part of a generalized infection. Early treatment of syphilis does much to prevent neurosyphilis and decreases the severity of symptoms when it does develop. Any treatment of early syphilis is preferable to no treatment at all. Even inadequate early treatment reduces the incidence of neurosyphilis and decreases the severity of symptoms when it does develop. The trend in treatment is earlier use of energetic fever-chemotherapy routines in all cases diagnosed as neurosyphilis. Neurosyphilis responds best to treatment in the asymptomatic phase. Spinal fluid studies are necessary for a diagnosis of asymptomatic neurosyphilis, and all cases should, therefore, have early spinal fluid examinations. Neurosyphilis is more common than was previously thought to be the case. Research work is indicated toward further increasing the efficiency of the treatment of neurosyphilis.

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PRELIMINARY REPORT ON INVESTIGATIONS OF BULLIS FEVER

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An apparently new clinical entity called Bullis fever occurred in mass outbreaks among troops stationed at Camp Bullis, Texas, in the summer months of 1942 and 1943 (Woodland, McDowell and Richards, 1943).

Laboratory investigations of human cases (Livesay and Pollard, 1943) have demonstrated a rickettsia-like organism as the probable agent of the disease, while the epidemiological observations pointed to the "Lone Star" tick (Amblyomma americanum) or mite (Trombicula) as probable vectors. No relationship between Bullis fever and any of the known human rickettsioses was found by the above authors.

In the present work initiated in July, 1943, five hundred adult specimens of **Amblyomma americanum** from Camp Bullis, Texas§, were divided in five batches of one hundred each and emulsions of each group of ticks inoculated into guinea pigs and Swiss mice. Out of one group of one hundred ticks, a strain of an infectious agent was established in guinea pigs and carried in passages. Guinea pigs reacted with fevers of various types and with splenomegaly. In mice the infection is manifested by splenomegaly only. Generally speaking, the symptomatology and pathological lesions produced by this strain correspond to those induced in guinea pigs and mice by human Bullis fever. The response of our guinea pigs to the infection is also somewhat similar to that observed by the Rocky Mountain Laboratory (Dr. Parker, personal communication, 1943).

An intracytoplasmic rickettsia invading lymphocytes and monocytes and similar to that observed in the strain of human origin (Livesay and Pollard, 1943) was established by the writers in various tissues of guinea pigs and mice infected with the strain of tick origin. Furthermore, guinea pigs convalescent from the infection induced by ticks proved immune to reinfection with the human strain†. No immunity to spotted fever or to Q fever was found.

It seems, therefore, highly probable that the rickettsia recovered by the authors from **Amblyomma americanum** of Camp Bullis, Texas, represents the agent of Bullis fever. Consequently, Bullis fever would be a new rickettsiosis conveyed in nature to man by **A. americanum** in addition to spotted fever and Q fever.

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STUDIES OF THE PROPERTIES OF THE A-V NODE: *I. RECIPROCAL RHYTHM; II. DRUG EFFECTS ON THE A-V JUNCTION.*

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Reciprocal rhythm (reciprocating rhythm, Wechselrhythmus, Umkehr-Extrasystole, return beat) is a rare disturbance of the cardiac mechanism; indeed, some authors have refused to accept most of the few cases that have been reported. We have recently made detailed observations in a patient who showed this mechanism over a period of several weeks. We had the opportunity to study electrocardiograms taken on numerous occasions and under varying circumstances. From these we have collected data sufficient to enable us (1) to propose a detailed concept of the physiological processes involved, and (2) to report the effects of various drugs, known to affect the heart, on these processes.

Twenty-two cases have been found in the literature which purport to represent reciprocal rhythm. In 1915 White described the electrocardiograms of a patient who showed an atrioventricular rhythm with retrograde V-A conduction. When the R-P interval was prolonged to approximately 0.30 seconds by digitalis administration or carotid sinus pressure, bigeminy resulted. In another patient with a similar mechanism (White, 1921) it was noted that shortening of the R-P interval by exercise or atropine injection might abolish the bigeminy. White concluded that the physiological mechanism operating in these hearts was analogous to that which had been observed by Mines in the frog heart, and which he had called a "reciprocating rhythm." In Mines' experiments auricular and ventricular contractions alternated in such a fashion that each contraction seemed to depend for its stimulus on the preceding contraction of the other chamber. He postulated that the impulse passed from the auricles to the ventricles in one set of communicating fibers and in the reverse direction through another group of fibers. By partial longitudinal division of the heart he was able to demon-

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strate such a circus mechanism, the stimulus passing down one side of the ring and up the other. He later was able to show that such a circus mechanism could be induced in a ring cut from the muscle of a single chamber of the heart. White's interpretation of his cases was based on the concept that the impulse arising in the atrioventricular junctional tissue stimulated both the ventricle and the auricles, the latter by retrograde conduction. When retrograde conduction was sufficiently slow the impulse might again pass to the conduction tissue and ventricle, producing the bigeminy.

Drury (1924) first employed the term reciprocal rhythm in his report of a case of A-V nodal paroxysmal tachycardia in which there was progressive prolongation of the R-P segments. Occasionally this led to retrograde block, analogous to the Wenckebach type of A-V block. On other occasions, however, R-P prolongation gave rise to reciprocal beats. R-P intervals from 0.126 to 0.147 seconds in duration were followed by reciprocal beats, while R-P intervals below 0.124 seconds were not. The R-P intervals of the reciprocal beats varied from 0.154 to 0.179 seconds, inversely with the length of the preceding P-R time. Wilson's (1915) figures show several examples of couplets which are probably reciprocal beats; these were recorded during periods of nodal rhythm which resulted from vagal stimulation shortly after atropine administration. Bishop (1921) recorded an instance of reciprocal beating, though he did not thus interpret his curves. His patient showed an A-V nodal rhythm with retrograde auricular stimulation. The administration of atropine produced frequent reciprocal beats. Jones and White (1927) reported two additional cases of nodal rhythm showing reciprocation. In their first case the retrograde P waves are sometimes positive, though usually negative. The second case shows short runs of five beats, in addition to the frequent bigeminy.

Dock (1928) published a careful study of a patient who had received a large dose of digitalis for the control of a paroxysm of auricular tachycardia. A nodal rhythm appeared as a sequel to this medication. Retrograde conduction time showed progressive prolongation, with ulti-

mate appearance of reciprocation. Relatively short R-P intervals were associated with long P-R intervals, and vice versa. The shorter P-R intervals were followed by aberrant QRS complexes which showed defective left bundle branch conduction, a peculiarity which enabled Dock to estimate the refractory period of the left bundle branch. Vagal stimulation in this patient slowed the nodal rate, but accelerated retrograde conduction, prolonging the P-R intervals and decreasing coupling. Administration of atropine increased the rate of the A-V node, delayed retrograde conduction and hence shortened the P-R intervals; coupling became more constant. Amyl nitrite produced no additional effect when given 30 minutes after the atropine.

Blumgart and Gargill (1929-30) reported four cases of reciprocal rhythm, the first of which was intensively studied. The R-P conduction time showed gradual progressive prolongation from 0.12 to 0.26 seconds. When the R-P interval was below 0.20 seconds there were no reciprocal beats. However, when this interval exceeded 0.26 seconds reciprocation occurred; hence the refractory period of the nodal tissue was between 0.20-0.26 seconds. Exercise and atropine shortened the R-P time and abolished the reciprocal rhythm; vagal stimulation prolonged R-P time so that reciprocal beats were more frequent; R-P prolongation was as much as 0.30 seconds, with P-R conduction as fast as 0.16 seconds. The inverse relationship between R-P and P-R conduction times was again noted. Epinephrine and physostigmine produced no changes. Reid (1930) published curves taken from a child five years after severe diphtheria, which show a nodal rhythm with variable retrograde conduction, and occasional coupling, due probably to reciprocal beats. Cutts (1937) described his studies of a patient with an interventricular septal defect who had an acute enteritis when first seen. Reciprocal beats were frequent during the time he had fever. Carotid sinus pressure, change in posture, and ingestion of cold water were without effect on the rhythm. Exercise increased the nodal rate, and no reciprocal beats occurred. Epinephrine accelerated the rate and shifted the pacemaker to the S-A node. Deep respiration

shifted the pacemaker down to the A-V node, and produced reciprocal beats. Digitalis in large dosage produced frequent reciprocation. Before digitalization atropine merely shifted the pacemaker from the A-V to the S-A node; after digitalization, the reciprocal beats present were abolished by atropine. Cutts also noted the general inverse relationship between R-P and P-R conduction times.

Gallavardin (1914) described two cases with nodal rhythm in whom ocular pressure or atropine produced a bigeminy. He regarded the second beat of the couplet as a normal beat of supraventricular origin, but discarded the possible interpretation of reciprocation. Gallavardin and Gravier (1921) reported an instance of A-V nodal rhythm with retrograde conduction to the auricles, in which vagal stimulation prolonged the R-P interval, producing reciprocal ventricular beats. Gravier et al. (1939) discuss another similar case which they believe showed two possible types of coupling: (1) true reciprocal rhythm with negative retrograde P waves, and (2) bigeminy due to positive P waves of sinus origin falling just at the end of the ventricular refractory period and conducted to the ventricle.

Wolferth and McMillan (1928-29) describe a unique case of 2:1 heart block which they interpret as showing occasional reciprocation with the pathway auricle-ventricle-auricle, the reverse of that described by others.

The interpretation of the cases mentioned above as instances of reciprocal rhythm is not unchallenged. Luten and Jensen (1931-32) emphasize the possibility that many of the cases described are examples of an auricular parasystole. Ziesler (1932-33) regards nearly all the reported cases as actually representing instances of interference dissociation. Of all the cases published before the time of his paper, he accepts as probably correct the single couplet shown by Gallavardin (1921), and as definitely reciprocal rhythm only the cases of Drury and Bishop. He is correct in stating that the published curves are often insufficient basis for a clear differentiation, but we doubt his justification in ruling out the possibility of reciprocal rhythm on these strips, when longer curves have been otherwise interpreted by competent authors. That the

opposite error in interpretation is equally likely, we will later show.

The circulating reciprocating mechanism described by Mines, when once initiated, persisted until interrupted by a premature stimulus. None of the clinical cases reported clearly show more than one circle, giving a bigeminy, though in Scherf's dog experiments a trigeminy could be obtained. Purported exceptions to this generalization are cases reported by Fischer (1929) and Samojloff and Tschernoff (1930), who interpret their curves as illustrating a continuous reciprocal rhythm. This possibility cannot be denied, though their published curves give little support to their contention, and certainly do not prove it. Theoretically, there seems to be no clear reason why a continuous reciprocal mechanism should not exist; such a possibility might explain some of the poorly understood physiologic disturbances of the heart. In fact, the underlying mechanism of paroxysmal tachycardias in general is thought by Barker and Wilson (1943) to be related to a circus mechanism involving the A-V node.

Scherf (1941) has recently discussed his experimental studies of reciprocal rhythm. Ischemia, clamping and cooling were used to depress the activity of the S-A node; after the A-V nodal tissue assumed the role of pacemaker, quinidine administration or left vagal stimulation produced the delay of R-P conduction requisite for reciprocation. In the dog several phenomena were noted which thus far have not been seen in clinical cases: alternation of the R-P interval, triplets with two sequential reciprocal beats, and interpolated reciprocal beats. Scherf offers these findings as evidence for longitudinal dissociation of the A-V node.

Levin (1941) has recently described a unique case in which reciprocal beats followed not only impulses of A-V nodal origin, but, rarely, also followed what appear to be ventricular premature beats. With the latter the RP interval is unusually short, a fact explained by the author on the basis of "Bahnung" (Skramlik, 1920). Bain (1938) has also published a brief report of a possible instance of reciprocation.

Clinical Cases

In the files of the Heart Station are five cases whose tracings have justified the consideration of a reciprocal rhythm. They illustrate from the electrocardiographic standpoint the difficulties of proving the presence of this mechanism.

Case 1. H. W., Col. male, age 43, John Sealy Hospital, J. S. H. No. 42285*, was admitted Sept. 30, 1934, because of a stab wound of the right lower abdominal quadrant. Exploratory laparotomy showed no damage had been done to the viscera. On the fifth postoperative day he experienced intense precordial pain, associated with perspiration, fever to 101°, many premature cardiac beats, and a blood pressure drop to 110/80 from a previous level of 150/120. A clinical diagnosis of coronary artery thrombosis was made, and was supported by atypical serial electrocardiographic change. On the day of the attack of precordial pain there was a sinus rhythm. On Oct. 6th and 9th there was an A-V nodal rhythm with frequent bigeminy. This persisted through Oct. 25th. Morphine sulphate was the only medication used.

* John Sealy Hospital unit history number.

Case 2. J. G., Col. male, age 48, J. S. H. No. 43593, was admitted March 29, 1934, in congestive heart failure. Blood pressure was 145/55; there was a free aortic insufficiency due to syphilitic aortitis. The first break in cardiac compensation had occurred in January 1934, and failure had appeared again in February. His symptoms had been relieved by the administration of nitroglycerine and aminophylline. The electrocardiogram taken March 30th showed a nodal rhythm, with frequent coupling. The patient died April 2nd; at necropsy the heart weighed 600 gm; there was syphilitic aortitis partially occluding the left coronary ostium, and valvulitis with extensive damage to the aortic valve leaflets. Marked chronic passive congestion was evident in the lungs and abdominal viscera.

Case 3. N. M., Col. male, age 60, J. S. H. No. 44359, was admitted Aug. 19, 1935, because of congestive heart failure. He had been seen on three previous hospital admissions, each because of cardiac failure. The etiological factor in this patient's heart disease was arteriolar vascular disease, with hypertension. The blood pressure levels had approximated 200/140 since 1930 and digitalization had been begun at that time and maintained intermittently since.

When admitted in August 1935, he had been taking two gr. iss tablets of digitalis daily since the preceding May and this dosage was continued in the hospital until it was reduced to one tablet daily on August 23rd. The electrocardiogram shown in Fig. 1 was taken on the 23rd. Improvement was shown in the patient's cardiac status, and he was discharged September 6, 1935. He had two subsequent admissions, and died September 18, 1936. At necropsy the heart weighed 620 gms. There was marked clacification of the aortic root, with virtual oblitera-

tion of the right coronary orifice, and marked narrowing of the left. There was marked generalized chronic passive congestion and moderate renal arteriosclerosis.

Case 4. N. W., Col. male, age 52, J. S. H. No. 48615, was admitted first on July 22, 1935. He had been under observation because of syphilitic aortic insufficiency since 1930. Subsequent evidences of cardiac failure had appeared in January 1935. He left the hospital without permission in 1935, and was not seen again until he applied for readmission January 28, 1939. Examination showed again a free aortic regurgitation of syphilitic etiology. The blood pressure was 200/55; venous pressure 32 cm. Digitalization was begun, and was maintained until March 3rd. On February 27th an auricular flutter developed, which responded to 30 gr. quinidine given on March 3rd. On the next day a bigeminy was recorded for the first time, a mechanism which persisted intermittently until the patient's death 18 months later. He was maintained in the out-patient clinic on daily rations of digitalis and frequent injections of mercurial diuretics. Cardiac failure was severe enough to require hospitalization in August 1939 and again in September 1940, at which time he died. Necropsy showed a heart which weighed 760 gms, with marked enlargement of both the right and left chambers. There was syphilitic aortitis and valvulitis with aortic insufficiency; in addition there were quadricuspid pulmonary valve leaflets and an apparently congenital defect of the tricuspid ring and aortic leaflet of the tricuspid valve, which produced a marked tricuspid insufficiency. The coronary arteries were not abnormal. Extensive chronic passive congestion was evident throughout the body.

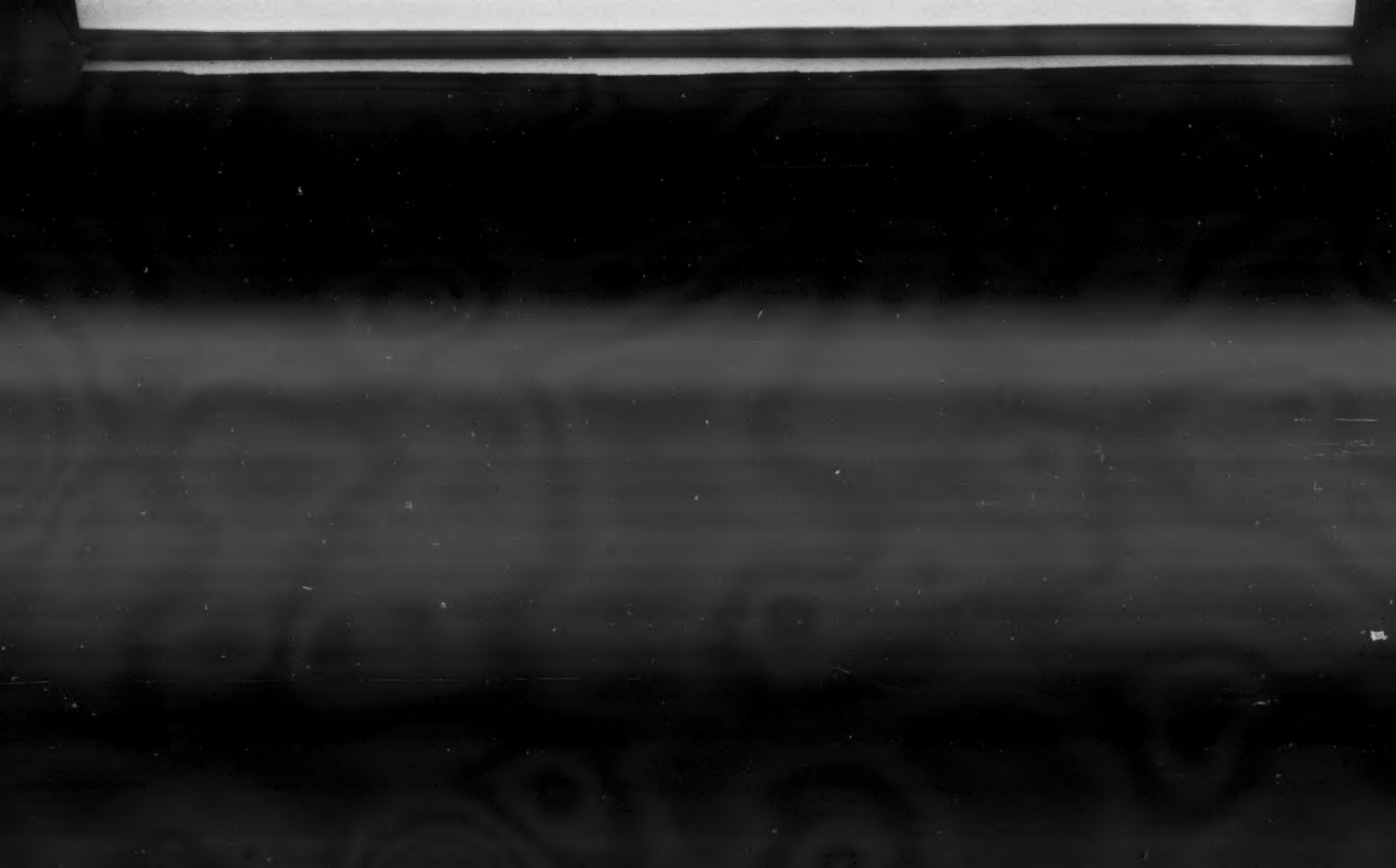
Case 5. G. C., Col. female, age 51, J. S. H., No. 49257, was admitted January 16, 1943. Hypertensive heart disease with a blood pressure of 250/118 and syphilitic aortic regurgitation had first been noted in 1936. Since that time she had received extensive antiluetic therapy. Cardiac failure had been manifest for the first time in 1939; she had been hospitalized at that time, and again in 1941. When admitted in January 1943 congestive heart failure of moderate grade was again present; the venous pressure was 15 cm. and the circulation time with magnesium sulphate was 20 seconds. The heart was greatly enlarged, and there were the usual signs of pulmonary and hepatic congestion.

Digitalization was begun on January 19th, and maintained through the 30th. Early electrocardiograms had shown a sinus rhythm, with what was thought to be a variable S-A and A-V block. The nodal rhythm persisted, although digitalis dosage was reduced. Because of the low amplitude of the auricular complexes, tracings were taken with an esophageal electrode for the purpose of obtaining clear P waves. It was from these curves that the presence of a reciprocal rhythm was established. During later studies, because of the discomfort associated with the use of the esophageal electrode lead CF_1 was used, modified by placing the chest electrode in the third interspace just at the right sternal border. This lead gave P waves which were satisfactory, though inferior to those obtained from the esophagus.

The details of medication and the effects on the cardiac mechanism will be discussed later.

Segments of the electrocardiographic tracings from each of these five patients are shown in Fig. 1. That for Case 1 shows an A-V nodal rhythm with a rate varying from 90 to 100 per minute. The P wave is lost in the QRS complex of one beat, may be seen with an R-P interval of 0.10 sec. in the next beat, and shows a longer R-P time of 0.15-0.18 sec. in the third beat; with the latter there is reciprocal beating of the ventricle, with aberration of the QRS complex. In Case 2 there is an A-V nodal rhythm with a rate of from 57 to 64 per minute; there is an apparently independent auricular rhythm, with a rate of 60 per minute. Most of the P waves appear to be blocked, but two of them are clearly conducted to the ventricle, with aberration of the QRS complex. The following R-R interval is somewhat less than that of the usual nodal rhythm. This is then an example of A-V dissociation with interference. In Case 3 there is no regular auricular rhythm to be found; in fact it is clearly absent, and hence this is a reciprocal rhythm, with two return beats shown. Case 4 shows an A-V nodal rhythm at a rate of 73 per minute; there is an independent auricular rhythm with a rate of 36 per minute. The first P wave shown on this strip is conducted to the ventricle, giving one couplet; the other P waves are not conducted to the ventricles, the nodal rhythm being undisturbed by their presence. This is an example of A-V dissociation with occasional interference; it might be interpreted as representing an auricular parasystolic focus. Case 5 shows the absence of a regular auricular pacemaker; it is further discussed below.

The first requisite for the existence of a reciprocal rhythm is the location of the cardiac pacemaker in the A-V node. This requirement is satisfied by each of these five cases. The second prerequisite is the clear demonstration that retrograde conduction is present, and that the auricular stimuli do not arise in an independent auricular focus, from which they are conducted to the ventricle; when such a slower auricular pacemaker is present, some of whose impulses are conducted to the ventricle during the periods in which the conducting tissues are responsive, an interference dissociation will appear; similar curves may be interpreted as showing a parasystolic auricular focus. The clear proof of the presence or absence of retrograde conduction, or of the existence of an independent auricular pacemaker, is not always easy, and on the short strips that may be easily reproduced for publication, the true situation may not be apparent. This fact lends apparent support to Ziesler's contention that most of the published cases of reciprocal rhythm really show a regular independent auricular rhythmic focus. In most instances, the published tracings are inadequate to prove or disprove it. We suspect that the opposite error is equally likely, for where there is a regular A-V nodal pacemaker, with fairly regular retrograde conduction, with reciprocal beating, the tracing will show superficially the presence of fairly regular auricular complexes, suggesting the possible existence of an auricular pacemaker. Some strips taken on our patient showed such an apparent existence of an auricular pacemaker; others showed clearly its absence, which was confirmed by other circumstances which we will demonstrate.



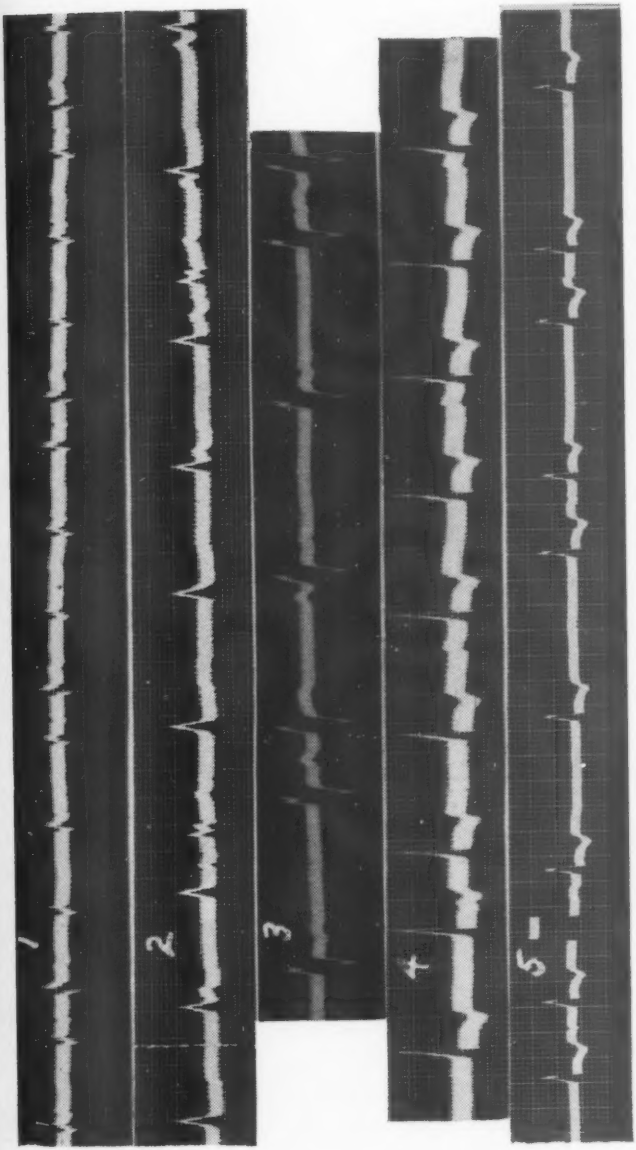


Figure 1. Strips from electrocardiograms of Cases 1–5, from above downward. See text for explanation.

Electrocardiographic Study of Case 5

Curves were taken on numerous occasions, at first with the esophageal electrode, later with a chest lead. Each curve contained the cardiac complexes for periods of from six to ten minutes. It was soon apparent that a regular A-V nodal pacemaker was present, and that variable retrograde conduction time to the auricles occurred. When the retrograde conduction time, measured approximately by the R-P interval, was short, the cycle terminated. However, when

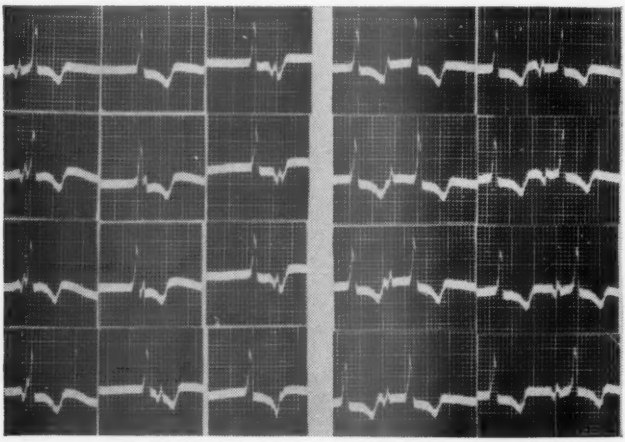


Figure 2. Selected complexes from the tracing taken Feb. 25, using the esophageal electrode. Gradual shortening of the P-R interval is seen, with emergence of a retrograde P wave. When the R-P interval exceeds 0.285 sec. reciprocal beats occur. Note the inverse relationship the R-P and P-R intervals.

this interval was longer, the impulse returned to the junctional conduction tissues, and again stimulated the ventricles. (Fig. 2). The absence of an auricular pacemaker may be verified by measurement of any of the curves reproduced herewith. (Cf. Fig. 3.) By measuring many complexes with a hand lens, we were able to show that on each occasion there was a clear-cut *refractory period*, during which the conducting pathways failed to conduct the forward impulse. This indicates that the retrograde impulse so influences the conduction tissue that it is refractory to a returning forward stimulus. This is illustrated in Fig. 4. Here all the complexes in a long strip of curve are represented. It will be seen that where the

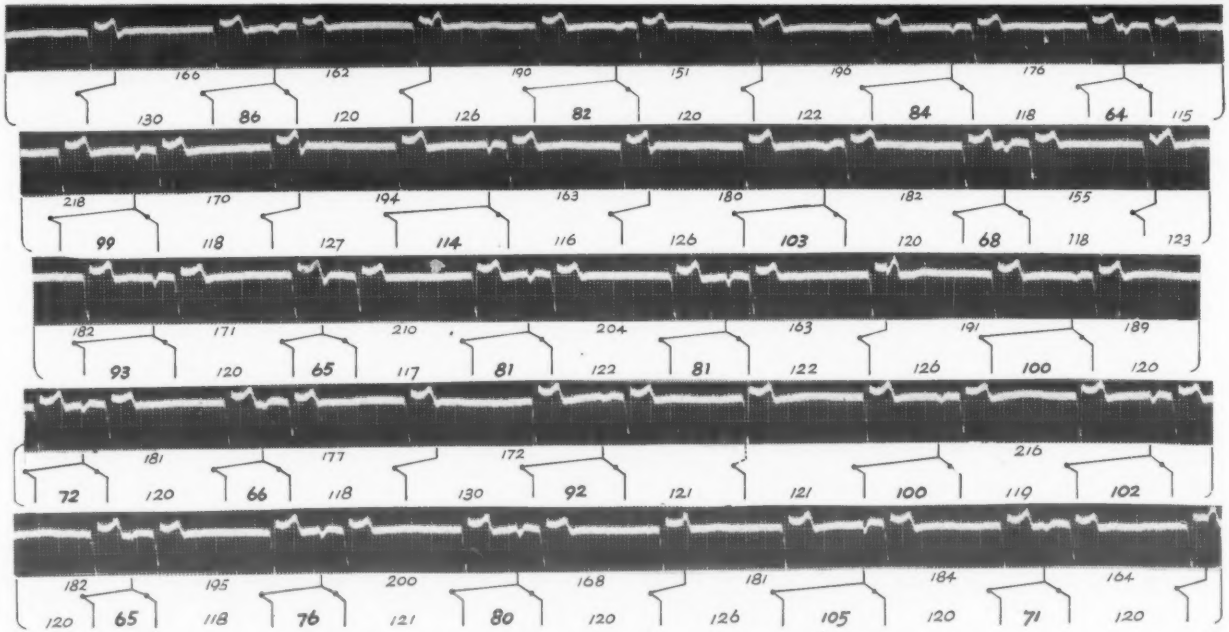


Figure 3. A continuous section of curve, taken March 4. Below each complex the impulse pathway has been diagrammed in the conventional fashion, showing its origin in the A-V node with conduction to the ventricle (QRS) and auricle (P). When reciprocal beats occur, the impulse passes again through the node to the ventricle. The P-P intervals show the absence of an auricular pacemaker, and the R-R intervals indicate that the returning impulse discharges the A-V node.

retrograde conduction time is below 0.26 sec. there is no reciprocal beat; however when the retrograde conduction time exceeds 0.26 sec. there follows a reciprocal stimulation of the ventricle. Thus, on this day, the absolute refractory period of the junctional tissue to forward conduction was 0.26 seconds.

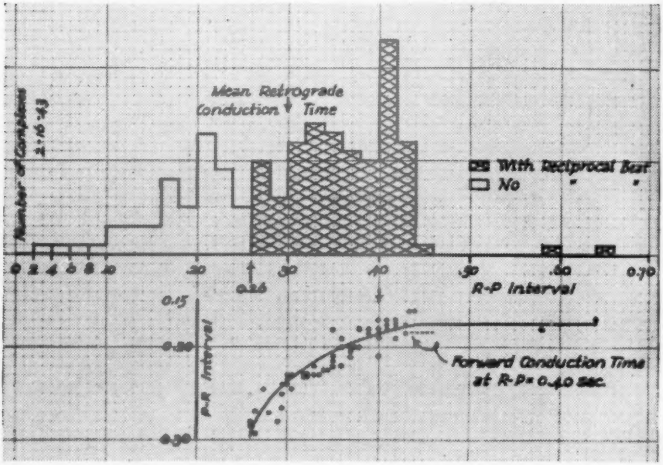


Figure 4. This diagram contains all the data obtained from the tracing taken Feb. 16. All R-P intervals are charted, at 0.02 sec. intervals, those associated with a reciprocal beat being cross-hatched. The refractory period of the nodal tissues to forward conduction is 0.26 sec.; the mean retrograde conduction time 0.30 sec. Below are charted the corresponding P-R conduction times, giving the curve of recovery of conductivity. By 0.44 sec. recovery is complete, with A-V time of 0.175 sec. For purpose of comparison the P-R interval at R-P 0.40 sec. is measured; here it is 0.185 sec.

A period of *relative refractoriness* may also be discerned. It may be noted, as others have done, though in less detail, that the shorter R-P intervals are followed by longer P-R intervals. When these associated values are graphically represented, and a smooth curve drawn through the points, one may note immediately the resemblance to the recovery curves illustrated by Lewis and Master (1925-26), Ashman (1925), Ashman and Herrmann (1925-26), and Drury and Regnier (1927-29). Hence the absolute refractory period is followed by a period of *recovery*, during which the tissue is relatively refractory, but will conduct more slowly. Our curves are strictly analogous to the recovery curves obtained by Lewis and Ashman in

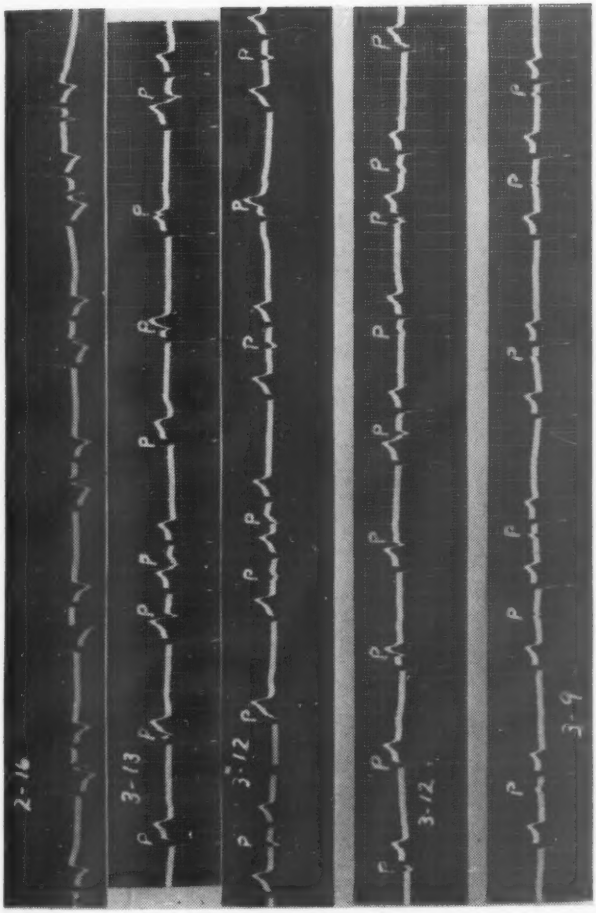


Figure 5. Triplets: first strip, Feb. 16, esophageal lead; second, March 13; third, March 12; fourth, March 12, showing both a triplet and a double pathway from node to auricle; fifth, March 9, two hours after 3 grains of quinidine.

their animal experiments, and to the single curve obtained by Ashman and Herrmann in a human case of heart block. One such curve is plotted in Fig. 4. Here the A-V nodal tissue is absolutely refractory up to 0.26 sec.; recovery of conductivity takes place from 0.26 to approximately 0.44

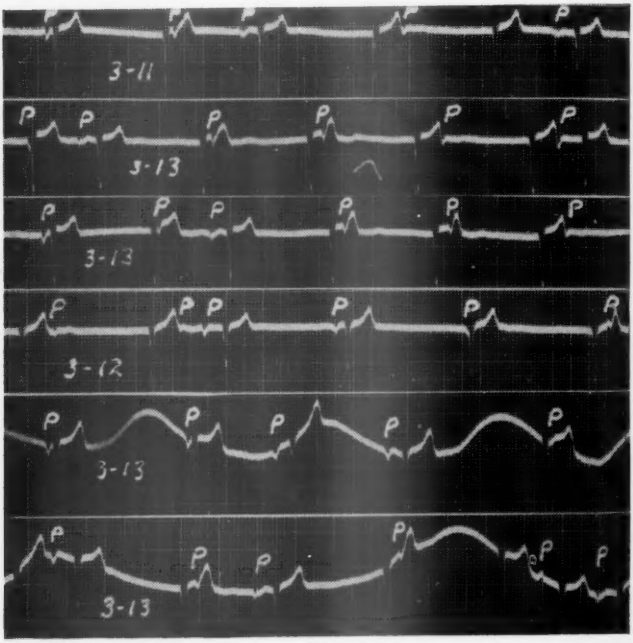
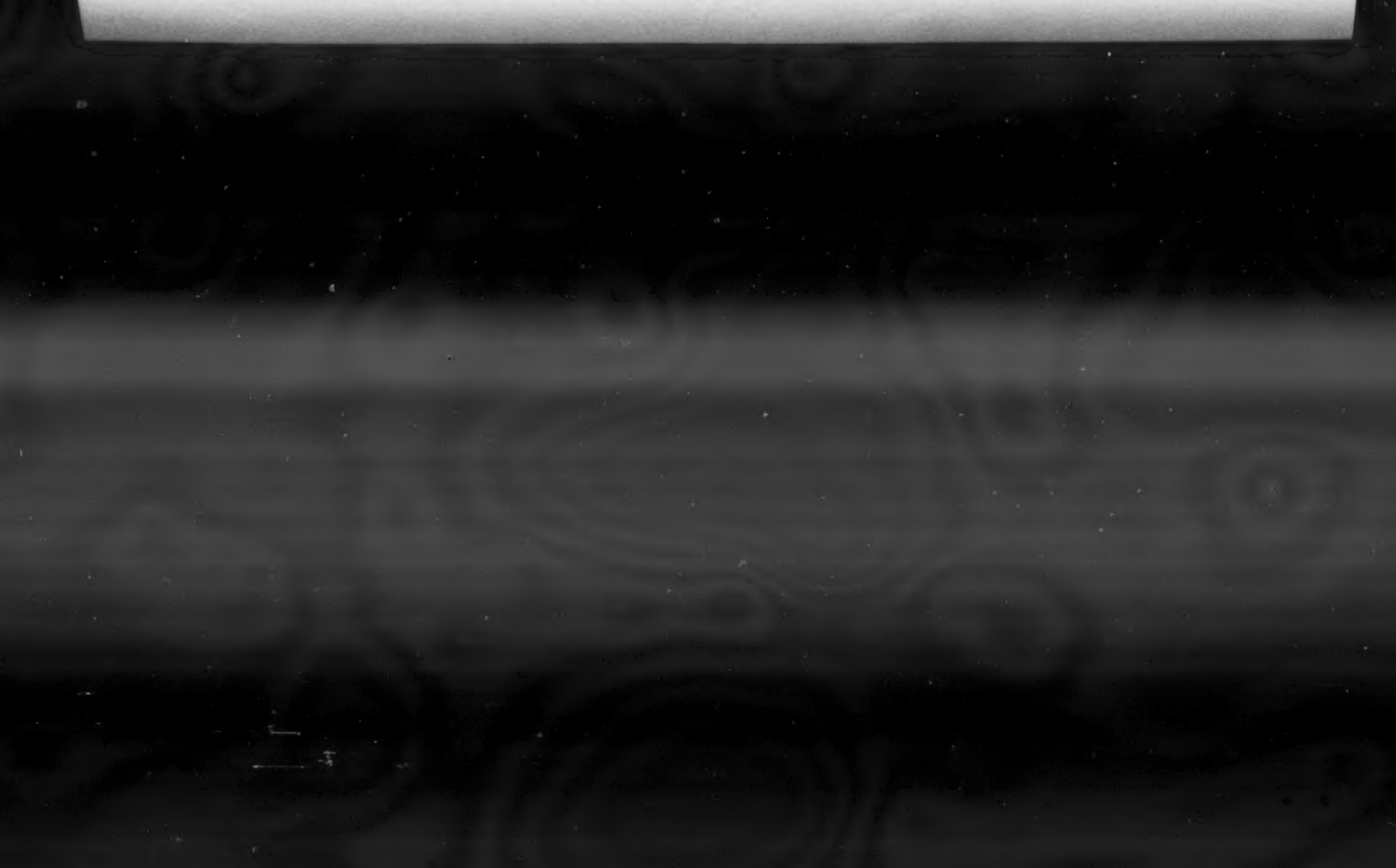


Figure 6. Double pathway from node to auricle (see text). P. waves are marked, and show in each instance one auricular complex due to rapid retrograde conduction, and another due to slower retrograde conduction and associated with a reciprocal beat. From above downwards: 1. March 11, after neosynephrine; 2, 3. March 13, control curve; 4. March 12, two hours after 5 grains of quinidine; 5, 6. March 13, immediately after injection of mecholyl, followed by atropine.

sec. During the period 0.26-0.44 sec. the tissue is relatively refractory, and conduction takes place, but takes longer than the 0.175 sec. conduction time after full recovery. The reaction of refractoriness, conductivity, and recovery to various drugs will be detailed in the following section.

Triplets were obtained by Scherf in his experimental study of reciprocal rhythm, though they have not hereto-



fore been seen in human cases. We found numerous triplets, which were most numerous during the latter part of the period of study, when the patient was well digitalized. These represent two sequential reciprocal beats, in which the stimulating impulse makes two complete circles instead of one. In Fig. 5 we show a few examples of this mechanism, which under certain circumstances was very frequent. We would expect to find that equally common would be complexes in which the auricle was stimulated twice, with the second auricular impulse failing to reach the ventricle. Actually, we could find only two such complexes, shown in the two lower strips of Fig. 7. The lower strip in Fig. 5 may give some hint as to why, although triplets were common, higher multiples of the circus mechanism were not seen. This lies in the divergence of the P-R intervals in the triplet from the recovery curve drawn from the whole strip (compare with the accompanying couplets). The first P-R in each triplet is unduly long, the second is short. This initial delay in forward conduction may permit of recovery of the retrograde pathway, and allow the impulse to return again to the auricles. The second P-R interval shows more rapid A-V conduction, probably illustrating the presence of facilitation of conduction, (the "Bahnung" of Skramlik or "treppe of conductivity" of Askman). The rapidity of forward conduction in the second instance probably does not allow of adequate recovery of the retrograde pathways, and hence the circus movement is interrupted.

Double auricular pathways were seen perhaps a couple of dozen times. We reproduce seven representative examples: one in the last couplet of the fourth strip in Fig. 5, and one in each strip of Fig. 6. In each instance there is evidence of rapid retrograde conduction with R-P time short or even negative; in addition there is a longer R-P interval associated with a reciprocal beat. For example, in the first complex referred to above (Fig. 5, strip 4), the first P wave shows very rapid retrograde conduction, with a negative R-P time, producing a complex identical with the first one on the same strip; the second P wave arising apparently from the same focus has a longer R-P interval, exceeding the junctional refractory period,

and allowing of reciprocation. In this case, the second P wave is identical with the one just preceding the couplet under discussion. On some occasions, the first P wave is more easily seen than the second or slower one, but the latter's presence may be certainly deduced by the presence of reciprocation. In each of the examples illustrated, there is no doubt of the existence of the double auricular pathway from the A-V nodal pacemaker, with the production of two retrograde P waves.

We at first thought this concept an original one, but later discovered that it had also been employed by Danielopolu and Proca (1926) to explain the findings in their case of nodal rhythm. They support their concept, which is similar to ours, with anatomical diagrams which find support in the histological studies made by Kung and Mobitz (1930) of the auricular ramifications of the human A-V node.

The pathway of the returning stimulus was thought by Mines to be in the same conducting system that carried the retrograde impulse. He conceived that while one group of fibers was refractory, a second group was sufficiently recovered to be able to conduct. When retrograde conduction was accomplished, the first group had recovered sufficiently to transmit the impulse downward, and so on. The absence of change in the P wave indicated to Drury that no circus mechanism involved the auricle, and he placed the turning point of the impulse in the upper part of the A-V node. He stated that the rhythm of his case was undisturbed by the reciprocal beat, though actual measurement of his records show, interruption of the rhythm through discharge of the ectopic focus by the reciprocal beat; immediately afterwards the rhythm was resumed at the original rate. The concept that one group of fibers conducted upwards and one forward has been generally adopted. Scherf and Shookhoff (1926) first proposed the idea that there was actually a functional longitudinal dissociation of the nodal tissue; this has been accepted by Fischer (1929) and by Rothberger (1931), and Scherf has recently adduced further experimental support (1941).

The published curves however, and ours as well, do not support the idea of longitudinal dissociation, with the

exception noted below. In nearly every instance, measurement will show that the returning impulse discharges the nodal pacemaker, and that the nodal cycle begins anew from the last beat of the couplet, or of the triplet. Several facts indicate to us that the same tissue, if it does not conduct, at least is *affected* by impulses going in both directions:

1. The reciprocal beat discharges the nodal pacemaker. (Fig. 3.)

2. The presence of a definite clear-cut refractory period during which return conduction does not occur. (Fig. 4.)

3. The curves relating R-P to P-R intervals, indicating recovery period of previously active muscle. (Fig. 4.)

4. Alternation of the retrograde P waves, and the occurrence of various forms of P waves (Fig. 7); alternation of the R-P interval (Fig. 7).

5. The occurrence of double pathways from the nodal pacemaker to the auricles, in the same couplet (Fig. 6).

6. Triplets (Fig. 5).

We do not wish to deny the existence of longitudinal dissociation as a general rule, only to propose an essentially similar mechanism. Certainly the curves shown by Scherf (1941), particularly those illustrating interpolated return extrasystoles, require the assumption of some type of dissociation, at least of a protective block of the nodal pacemaker. In most instances however, the discharge of this pacemaker by the return beat indicates that if some sort of dissociation is present, it is above the level of the pacemaker. This may readily be borne out by measurement of the published curves (Cf. Fig. 3).

Alternation of the R-P interval (Fig. 7, strip 1) may of course be explained on the basis of retrograde conduction over a single pathway. Other findings require the assumption of multiple pathways. It was frequently noted that the P waves varied greatly in a single long tracing in amplitude, direction, and conformation. Striking changes in the auricular complexes suggest strongly that the impulse pursues a variable pathway in the auricle. Alter- of the impulse through the auricular muscle in opposite nation in direction (Fig. 7) particularly indicates the spread

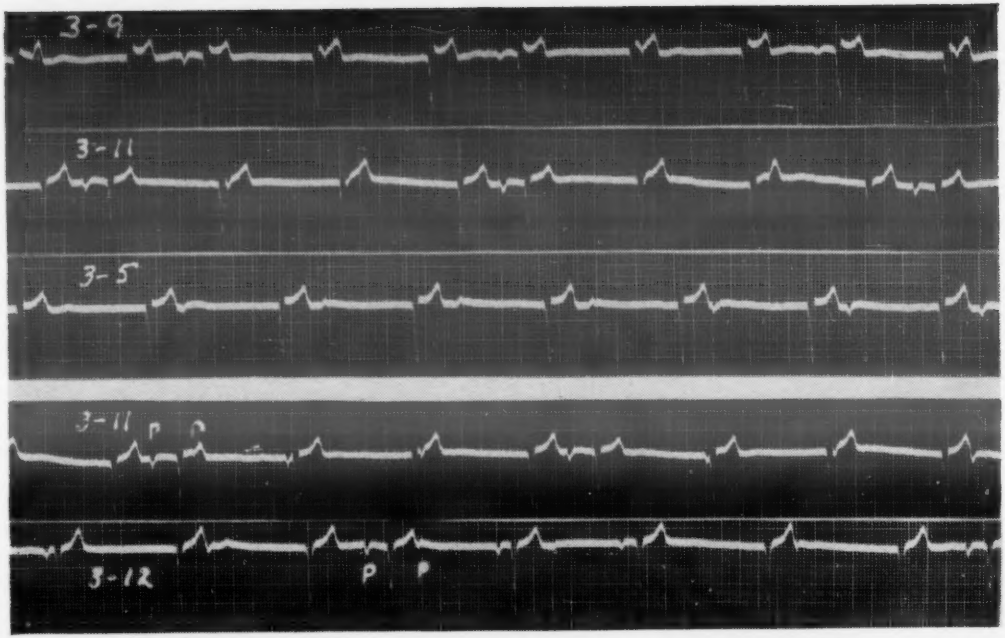
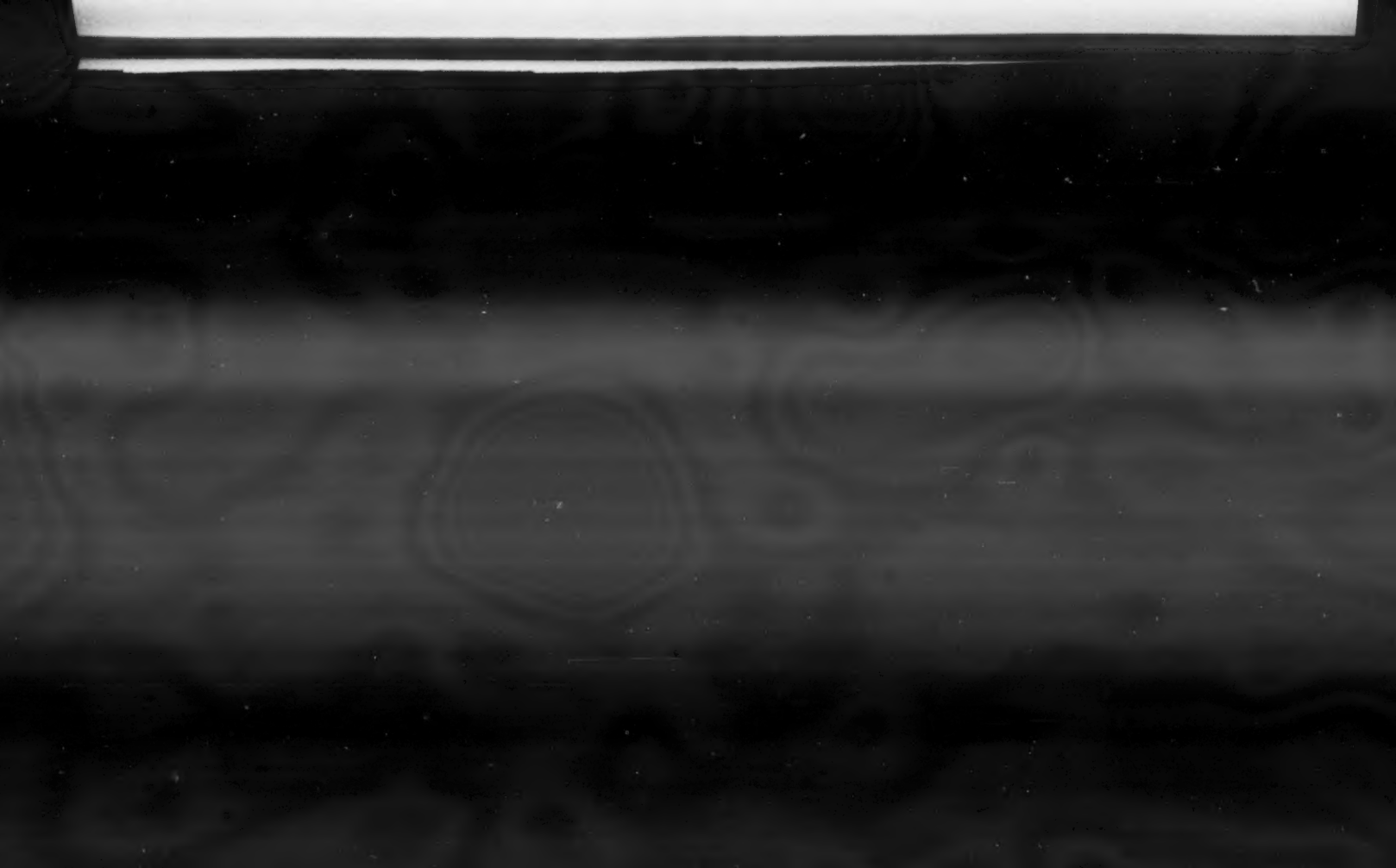


Figure 7. From above downwards: 1. March 9, alternation of R-P interval; 2. March 11, after neosynephrine, two short R-P intervals alternating with one longer one with reciprocation; 3. March 5, after prostigmine, variation in positive and negative P waves; 4. March 11, after neosynephrine, showing a P wave after the reciprocal beat; 5. March 12, two hours after 5 grains of quinidine, also showing a P wave following the reciprocal beat.



directions; one possible cause of such a variation would be the entrance of the impulse into the auricle at varying points. Such a possibility offers the only apparent explanation for the observation of two auricular complexes associated with a single couplet, strong evidence for the existence of multiple pathways from the nodal pacemaker to the auricle.

We venture to propose the concept that above the pacemaker, near the junction of the nodal tissue with that of the atrium, or more likely at the junction of the atrial and ventricular portions of the A-V node, there is an area of refractory tissue of varying size and shape, and/or in varying stages of recovery, and through which conduction will take place in varying directions and at varying rates. Reference to Fig. 8 will illustrate this and compare it with Scherf's concept. Delayed conduction through tissue which is only partially recovered, and hence relatively refractory, has been demonstrated by Lewis and Ashman as noted previously. When a strand of tissue in this area has completely recovered, retrograde conduction is rapid, e. g., through pathway A. If in pathway A there lies, however, a portion of relatively refractory muscle, retrograde conduction will be delayed, and the R-P time will be prolonged. In the meantime, the stimulus has spread along other routes, such as pathway B, and has entered an area of greater refractoriness, or perhaps a larger area of relative refractoriness. Here the impulse is blocked or perhaps conducted in a decremental fashion (Drury, 1925-26); this tissue has been rendered, nevertheless, completely refractory by the blocked impulse, and hence pathway C is blocked to an impulse from above. When delay in A has been great enough, recovery, either partial or complete, of area BCD allows the return of the impulse as illustrated through pathway D, followed by unobstructed passage through the lower portions of the conducting system. It is well known of course that under most circumstances forward conduction is easier than retrograde conduction, and that the impulse might pass down through tissue which would not conduct a retrograde impulse. Progressive prolongation of the R-P interval would

result from increasing relative refractoriness of the tissue in path A.

Variations in the size and shape of the area of refractory tissue might allow rapid passage of an impulse via route A, with recovery of the auricular muscle in time to allow it to respond to a much delayed impulse which passed through route B, or perhaps route E, and which later re-entered the nodal tissue by forward conduction

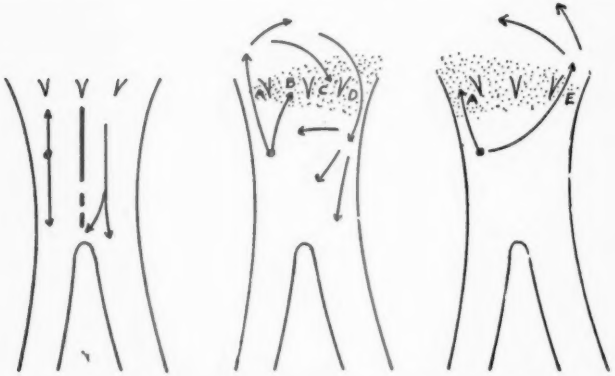


Figure 8. The figure on the left is taken from Scherf, and illustrates his concept of functional longitudinal dissociation. The middle and right diagrams illustrate the concept developed in the text.

down another pathway. We thus explain the double auricular stimulation described above. Analogous variations in the refractory area would explain as well the variation in direction and contour of the P waves, permitting us to assume that the retrograde impulse entered the auricles at different points along the junctional tissues, and hence pursued varying routes through the auricular muscle.

Finally, similar rationalization would allow an explanation of the fact that we have observed the frequent occurrence of the triplets, due, we believe, to two complete circles, e. g., A-D-A-D, or A-C-B-D. The influence of drugs upon the frequency of triplets, and the possible mechanism of their action will be discussed later. These concepts indicate the possibility that measurements of retgrade conduction are measurements of a property of one area of tissue, e. g., area A, while forward conduction,

refractoriness and recovery are measured in another area, e. g., B, C, or D, which is affected by, though it does not conduct the retrograde stimulus. It may also be understood that similar studies would be equally valid in cases of interference dissociation or of auricular parasystole, except that here retrograde conduction would not be present, and hence could not be measured. Ziesler (1931) has studied A-V conduction through junctional tissue rendered refractory by ventricular premature beats which were not conducted backwards to the auricle. Analogous recovery curves for human conduction tissue were also drawn by Ashman and Herrmann (1925-26) for their second case of complete heart block, which shows possibly A-V conduction during a supernormal phase of recovery.

The anatomical basis for human A-V conduction is a subject of current dispute. Although anatomical units have been described for the human heart which are analogous to those more easily demonstrable in lower animals, their existence has been denied by Glomset (1940). The question is one that assuredly deserves careful investigation. In lieu of a proven anatomical pathway—and it cannot be regarded as finally disproven—the existence of a functional pathway must be assumed. This assumption finds support in the observation of Hoff et al. (1939), who obtained adult type electrocardiograms from four-day chick embryos, which have in their hearts neither nervous connections, nor differentiated conduction tissues.

II. DRUG ACTION AT THE A-V JUNCTION

In the preceding section the simple method of study employed in a case of reciprocal rhythm has been outlined, and illustrated with respect to the determination of the refractory period of the junctional tissues, the relative refractory period of recovery, and the measurement of forward and retrograde conduction. Inspection of charts constructed from the electrocardiograms showed shifts which to permit comparison from day to day, necessitated the use of arbitrary measures of conduction. Thus in Fig. 9 it may readily be noted that the retrograde conduction times were longer after the administration of quinidine, and the recovery curves corresponding in Fig. 13 show delay in recovery of forward conductivity. We have

arbitrarily taken as representative of retrograde conduction, the mean, or average R-P interval observed. Also, for purpose of comparison, we have taken, as a measure of forward conduction, the P-R interval corresponding to

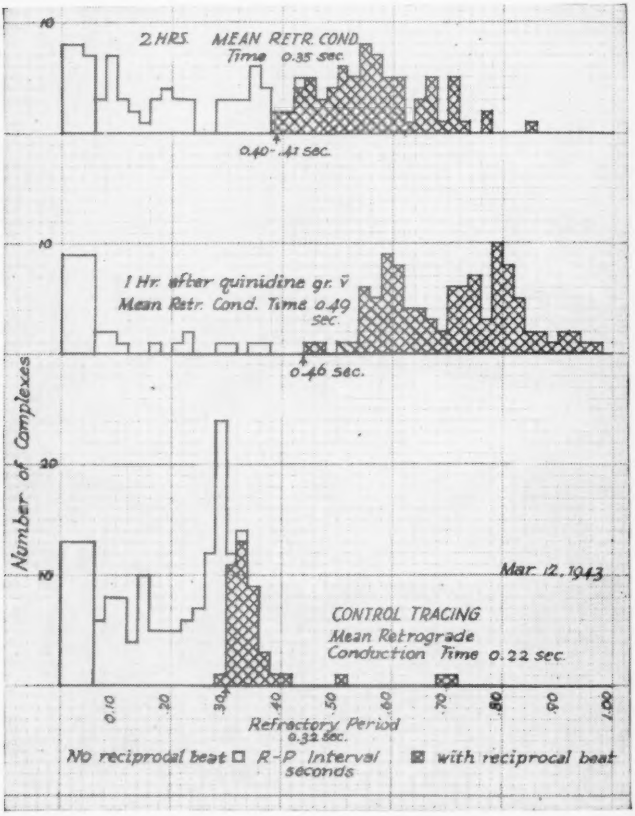


Figure 9. March 12, control, 1 hour, and 2 hours after 5 grains of quinidine. The diagrams illustrate the manner in which changes in refractoriness and retrograde conduction were calculated.

a preceding R-P time of 0.40 sec. This value is read from the recovery curves.

We have taken the opportunity to study the effect on the tissues involved in the reciprocating mechanism of drugs commonly employed for their action on the cardio-

vascular system. Carotid sinus pressure was employed as a means of reflex vagus stimulation but the relatively short period of pressure feasible, and the absence of conspicuous resulting change, led us to the use of mimetic drugs. During the period of time that we studied the patient she was receiving varying amounts of digitalis for the management of the cardiac failure which brought her to the hospital. Control tracings taken before the administration of the several drugs employed served also as an index of the effect of digitalis. She was also being given potassium iodide daily but we do not ascribe to it any influence on the results obtained. It is regrettable that more extensive observation could not be made, especially for the purpose of confirming the data obtained. This was however made impossible by the spontaneous disappearance of the reciprocal rhythm. We attempted to reproduce it, but our efforts in this direction were unsuccessful.

Many clinical cardiologists have been prone to accept as the physiological effects of cardiac drugs, especially of digitalis and quinidine, those given by Lewis in the last edition of his book (1925). Several texts on cardiology, and, actually, on physiology and pharmacology repeat these statements, apparently unaware that later work, some done by Lewis' group, have necessitated a change in viewpoint. It is worthwhile emphasizing also the fact that nervous and drug influences, determined or auricular or ventricular muscle, either in the intact animal or in isolated strips, cannot be taken as applicable to the A-V conduction system. Often the results at the two sites are widely divergent, or exactly opposite. Many questions concerning A-V conduction remain unsettled, ranging from the fundamental histological nature of human conduction tissue to the physiologically and clinically important nature of heart block of all varieties. In spite of the many careful studies directed towards its solution, the problem of A-V block is still a virtual mystery. Before presenting our own data on the effect of drugs on the tissues concerned in A-V conduction, it is necessary to assemble an outline of the information already available on the subject.

A-V junctional tissues. Conduction at the A-V junction is slower than elsewhere in the heart, the increasing order of rapidity being A-V junction, ventricular muscle, auricular muscle, and Purkinje fibers (Rothberger, 1931). Retrograde A-V conduction is even slower than that in the normal direction (Samojloff, 1922). Most of the A-V conduction time represented by the P-R interval of the electrocardiogram is occupied by delay at the node, relatively little being consumed by conduction through the auricles, or from the node over the His bundle and Purkinje fibers to the ventricular muscle (Wedd and Stroud, 1922). When A-V block occurs the defect lies in the A-V node, not in the responsiveness of the auricle or ventricle (Lewis, White and Meakins, 1913; Hering, 1910). The exact site of this conduction delay is not definitely known, but anatomical studies (Kung and Mobitz, 1930) suggest that it lies at the junction of the auricular and ventricular portions of the A-V node. The nature of the defect that gives rise to delay or failure of conduction at this point is not clearly understood, and the available information is too extensive and confusing to be detailed here. Unduly rapid rates with fatigue, anoxemia, nervous influences, local accumulation of acid metabolites, and local inflammatory or toxic injury are doubtless some of the factors which influence the excitability, responsiveness, and conductivity of the nodal elements. Still other factors may be operative under experimental conditions.

Vagus stimulation, both clinical and experimental, is well known to delay A-V conduction even to the extent of complete block; this may be obscured by the associated slowing of the auricular rate (Mines, 1914) or by displacement of the pacemaker of the heart to a point in or near the coronary region of the A-V node itself. Carotid sinus pressure may delay A-V conduction (Rothberger, 1931) and such reflex vagal stimulation, as well as mecholyl and prostigmine may produce high grade heart block, particularly when the auricular rate is rapid (Decherd, Herrmann and Schwab, 1943). Starr (1936) found the P-R interval prolonged by acetyl-B-methylcholine. Digitalis action is considered to be mediated, in part at least,

through the vagus. Atropine hastens conduction through the normal A-V node (Rothberger, 1931); rarely delay results because of an increased auricular rate. No effect is to be expected in A-V block of organic etiology.

Accelerator nerve stimulation hastens A-V conduction (Herrmann and Ashman, 1926; Danielopolu and Proca, 1926), though after exclusion of the S-A node by ischemia or cauterization this effect may be reversed (Fogelson, 1929). Moderate increase in auricular rate shortens the P-R interval; marked increase however, leads to prolongation of the conduction time (Lewis and Master, 1925-26), unless there is at the same time conspicuous vagal depression (Herrmann and Ashman, 1926). Exercise shortens the P-R interval if the heart is normal, but may prolong it when there is disease of the conduction system (Rothberger, 1931). Epinephrine may act by shortening the P-R interval, though sometimes increased auricular rate and paradoxical vagal stimulation may prolong it (Herrmann and Ashman, 1926).

Digitalis may accelerate conductivity in small doses (Clark and Mines, 1913; Weese, 1936), but the typical effect is delay, especially with full dosage. The latter is said to be abolished by pentobarbital (Van Dellen, Roberts, and Miller, 1942) which paralyzes the peripheral vagal ganglia. Extensive clinical and experimental evidence supports the view that the P-R interval is prolonged, occasionally to the extent of complete heart block. The mechanism of this digitalis effect is unsettled, though both vagal and direct muscular effects may play a role, with the latter probably more important.

Quinidine was found by Lewis, Drury, Iliescu and Wedd (1921) to delay A-V conduction; however, Starr (1936) found that quinidine prevented the production of this same effect by acetyl-B-methyl choline. Asphyxia, pressure and cold may delay conduction (Rothberger 1931) as may premature beats of either auricular or ventricular origin.

Retrograde V-A conduction is rare, though it may occasionally be seen when the cardiac pacemaker is in or below the A-V junction. When present it is usually slow when compared to conduction elsewhere in the heart.

Skramlik (1920) was able to produce it by properly timing ventricular stimuli in relation to a previous auricular beat, a phenomenon designated by him as "Bahnung." This may be due to a super-normal phase of conductivity during recovery of the nodal tissues from the preceding auricular impulse. Most ventricular premature beats do not show retrograde conduction.

Vagal stimulation usually prolongs the R-P interval, though its final effect on the frequency of reciprocal beats is variable (vide supra) since other factors, e. g., refractoriness, play a deciding role in the return of the impulse to the ventricle. Carotid sinus pressure and full expiration have similar effects. Physostigmine had no effect in one trial (Blumgart and Gargill, 1930). Atropine shortened the R-P interval in all the clinical cases of reciprocal rhythm in which it was used, though, as was true in the case of vagus stimulation, the effect on the frequency of reciprocation was variable.

Epinephrine accelerated retrograde conduction (Danielopolu and Proca, 1926), though it had no influence on one case of reciprocal rhythm (Blumgart and Gargill, 1930). Auricular premature beats interfere with a reciprocating rhythm (Mines, 1913; Rothberger, 1931); rapid ventricular rates may lead to a 2:1 retrograde block (Rothberger, 1931) or a retrograde Wenckebach type of block (Drury, 1924). Exercise, swallowing and forced inspiration produced the same effect as epinephrine (Danielopolu and Proca, 1926). White (1915) and Blumgart and Gargill (1930) also found exercise to shorten the R-P interval.

Digitalis delays retrograde conduction (Junkmann, 1925) and several observers have found it to prolong the R-P interval, either initiating reciprocal beats or make them more frequent.

Asphyxia produces a retrograde block (Lewis, White and Meakins, 1913-14); Scherf (1941) used vagal stimulation or quinidine administration to prolong the R-P interval in his dog experiments.

The *absolute refractory period* of conductivity of the junctional tissues is normally 30 per cent longer than that of the auricular muscle (Lewis, Drury and Iliescu, 1921). In cases of reciprocal rhythm it has been estimated at 0.11

to 0.26 sec. Though less marked than the effect on auricular muscle, vagal stimulation shortens the refractory period of the A-V node, according to Lewis, Drury, and Iliescu (1921), the accompanying delay in conduction being explained in terms of delayed recovery of excitability. Prolongation of the refractory period results from increased auricular rate according to Rothberger (1931), while Lewis and Master (1926) found shortening under these circumstances. There is evidence that it is prolonged by physostigmine and atropine (Junkmann, 1926) by digitalis (Lewis, Drury, and Iliescu, 1921; Junkmann) by quinidine (Lewis and Master; Junkmann) and by asphyxia (Rothberger).

The period of relative refractoriness or of recovery of conductivity has been studied in the A-V node only by Lewis and Master. When the rate is increased the curve begins earlier in the cycle, but rises less rapidly and its duration is prolonged; with more rapid rates recovery may be incomplete, and conduction becomes defective. Vagal stimulation and quinidine delay recovery and render it incomplete, and give rise to conduction with a decrement, leading to partial A-V block.

Supernormal recovery has been reported in the A-V junctional tissues by Lewis and Master (1924), by Ashman and Herrmann (1925-26), and Kline et al. (1939).

Although not directly bearing on the properties of the A-V junctional tissue, the corresponding properties of the *auricular and ventricular musculature* are perhaps of greater clinical importance, particularly in their intimate roles in the development, maintenance and cessation of several of the common cardiac mechanism disturbances. These aspects of the physiology of the heart have received a great deal of attention, though it must be admitted that a clear understanding of them has not been forthcoming. Here again the possibility exists that experimental data on cold-blooded hearts and on muscle strips cannot with validity be transferred to human subjects.

Conduction in the auricle is accelerated, and block relieved, according to Gaskell (1883), by vagal stimulation. Lewis, Drury and Bulger (1921) claim that vagal

stimulation was without effect upon conduction time, though when it was prolonged by rapid auricular rates of over 300 per minute, vagal stimulation reduced it to normal. In their opinion this effect was due to vagal reduction of the auricular refractory period. Vagal stimulation relieved the intra-auricular block produced by pressure or cold, and facilitated the passage of impulses which had previously been decrementally conducted (Drury, 1925-26).

Increased rates of auricular stimulation lead to defective conduction (Lewis, Drury and Iliescu, 1921). Asphyxia, compression, cold, fatigue and anoxemia all interfere with conduction in the auricles (Ashman, 1925).

Atropine slows auricular conduction, in part by counteracting the vagus effect; a direct muscular effect may also be detected, but this is ascribed by Lewis, Drury and Iliescu chiefly to the action on auricular refractoriness. These authors suggest a similar mode of action in the case of digitalis glucosides, their delay of conduction being most apparent with rapid auricular rates. However, Junkmann (1925) considered delay in conduction by digitalis to be a direct action, and this is supported by the recent work of Wedd, Blair and Dwyer (1941), who found the interference with conduction to occur later than the effects on refractoriness.

Quinidine was early noted to delay conduction (Lewis, Drury, Iliescu and Wedd, 1921), both by direct action and by abolishing vagal tone. This effect was considered at that time to be due to effects on the refractory period, but later observations indicate that the chief cause is a marked rise in the threshhold of excitability (Wedd, Blair and Gosselin, 1942).

It may readily be concluded that it is futile to make the attempt to separate conduction sharply from other properties of heart muscle. Conduction, refractoriness, excitability and recovery are all inextricably interdependent.

The *refractory period* of conduction has been the subject of extensive disagreement. It may be taken as well established that vagal stimulation shortens auricular refractoriness (Drury, 1925-26; Andrus and Carter, 1929),

and Lewis' group assign to this fact the chief role in the improved intra-auricular conduction noted after vagus stimulation, when this has been depressed by various means. Acetyl-B-methylcholine shortens the refractory period (Cohn and Macleod, 1939) but physostigmine produces no change (Junkmann). Atropine prolongs refractoriness (Lewis, Drury and Iliescu; Junkmann. The refractory period is in general shortened by increase in rate, though it may be prolonged relatively in very rapid rates. Junkmann (1925) found it prolonged by caffeine and adrenalin in spite of the associated acceleration of the heart, though this is disputed by Fogelson (1929) and Andrus and Carter (1929) actually found shortening after adrenalin.

Statements regarding the effect of digitalis and quinidine on the refractory period must be carefully qualified. It must be noted too that their direct effects may be modified by vagal ones, vagal stimulation and paresis being produced, respectively. Digitalis was long considered to prolong refractoriness. However, after Drury noted the phenomenon of decremental conduction (1925-26) he ingeniously modified his testing method so as to exclude conduction as a factor in his measurements of refractoriness. He and Love (1926) then found the absolute refractory period actually shortened by digitalis. That local refractoriness is so affected by digitalis has been confirmed by Macleod (1939) and Wedd, Blair and Dwyer (1941). Shortening of electrical systole, measured by the Q-T interval of electrocardiogram, after digitalization, has long been known to occur (Berliner, 1931; Cheer and Dieuaide, 1932). Lewis has admitted the truth of these findings (Lewis and Drury, 1926), but contends that measurements which depend on conduction, which he terms the "effective refractory period" are the ones pertinent to his concept of the circus mechanism of auricular flutter and fibrillation, and of the effect of drugs on this mechanism. Junkmann (1925) and Schellong (1931) also noted a shortening of the refractory period due to digitalis.

Quinidine prolongs the refractory period, according to the observations of Lewis, Drury, Iliescu, and Wedd (1921). Using Drury's method, however, Love (1926) found shortening instead. Junkmann (1925) states that prolonga-

tion of refractoriness occurs after quinidine, while Wedd, Blair and Gosselin (1942) found no change, ascribing the effects on conduction to the raised threshhold. Prolongation of the Q-T interval of the human electrocardiogram has recently been reported (Sagall et al., 1943).

Experimentally, cold, compression, fatigue, calcium, have been found to prolong refractoriness, and many other substances have been studied by Junkmann.

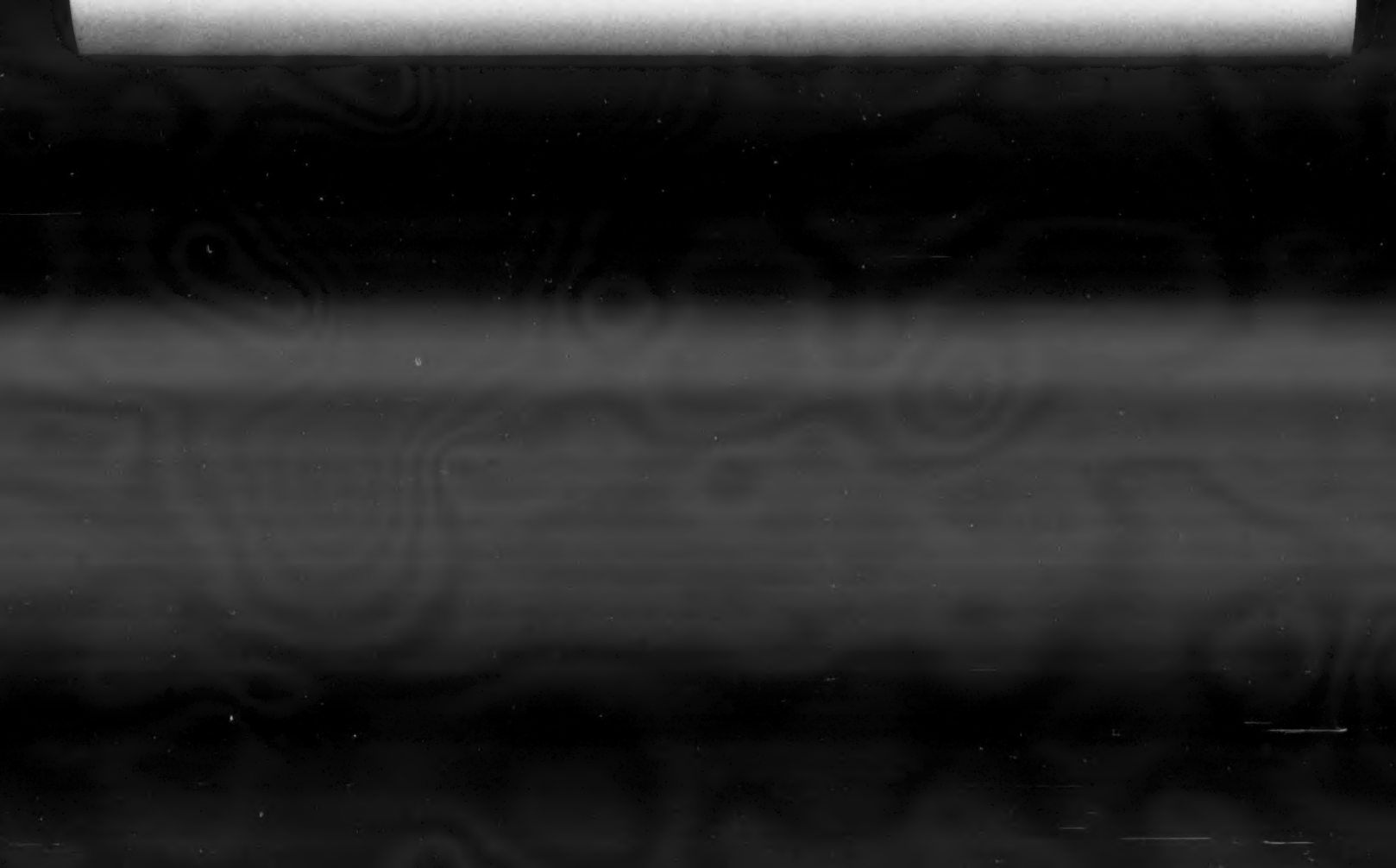
Recovery of conductivity, or the period of *relative refractoriness* has been little studied. Drury and Regnier (1927-29) found that vagal stimulation accelerated recovery in auricular muscle; this was slowed by quinidine, while atropine had no effect. Increases in rate were thought to expedite recovery. According to Junkmann however, the relative refractory period is shortened by muscle fatigue, and lengthened by digitalis, atropine and physostigmine. Schellong (1931) agrees that digitalis delays recovery.

A supernormal phase of muscular recovery has been found by Ashman, Seghers (1939), Junkmann, and Nahum and Hoff, (1939) but its existence is denied by Drury and Regnier, and Schellong.

EXPERIMENTAL DATA

Digitalis. The data obtained, and its association with digitalis dosage, are diagrammed in Fig. 10. Digitalis was administered as indicated in the form of tablets of the powdered leaf (Lederle) 1½ grains each, of U.S.P. XII strength. Accumulation of digitalis in the body has been calculated as usual, on the assumption that one tablet will be destroyed daily, additional amounts being retained. Because of the great individual variation, the curve obtained can at best represent an approximation, and since the patient was a small female, may well be too low; and the exact level at which the curve should begin is in doubt because of the uncertain effect of previous irregular digitalis dosage.

The method of estimating and graphically representing the data has already been described, and that obtained on February 16th illustrated in Fig. 4. The results obtained on other occasions have been treated in a similar fashion, and summarized in Fig. 10. It will be noted that digitalis prolongs the refractory period of the tissues involved, as



well as delays forward A-V conduction. The curves representing these factors parallel strikingly that showing approximate digitalis accumulation. When digitalis dosage was discontinued, both dropped disproportionately

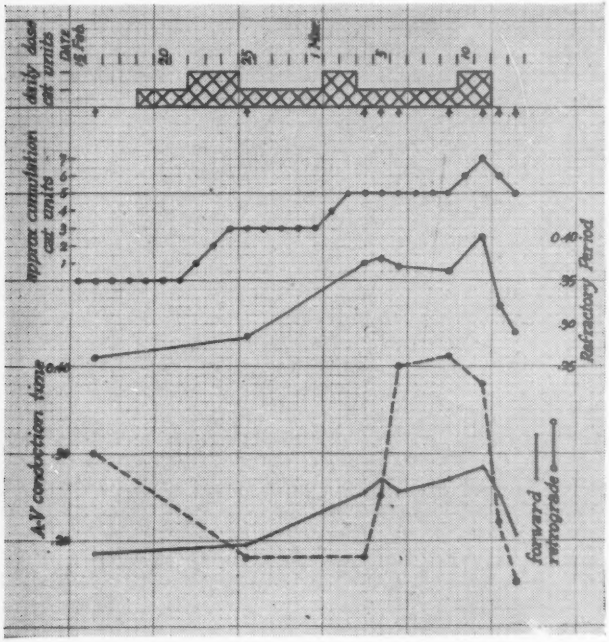


Figure 10. Effects of digitalis on the A-V node. Dosage of digitalis leaf, and approximate digitalis accumulation are charted. Below are shown the accompanying changes in the refractory period and in forward and retrograde conduction.

rapidly, suggesting that other factors may have been operative, an idea which is supported by the fact that resumption of digitalis administration failed to reproduce reciprocation. Retrograde conduction times behaved quite differently; with beginning digitalization backward conduction was, on the average, more rapid. Increasing dosage caused marked delay in retrograde conduction though this too fell sharply when the drug was stopped. This varying effect with smaller and larger dosage is reminiscent of the ob-

servations of Clark and Mines (1914) on forward conduction in the cold-blooded heart under similar conditions.

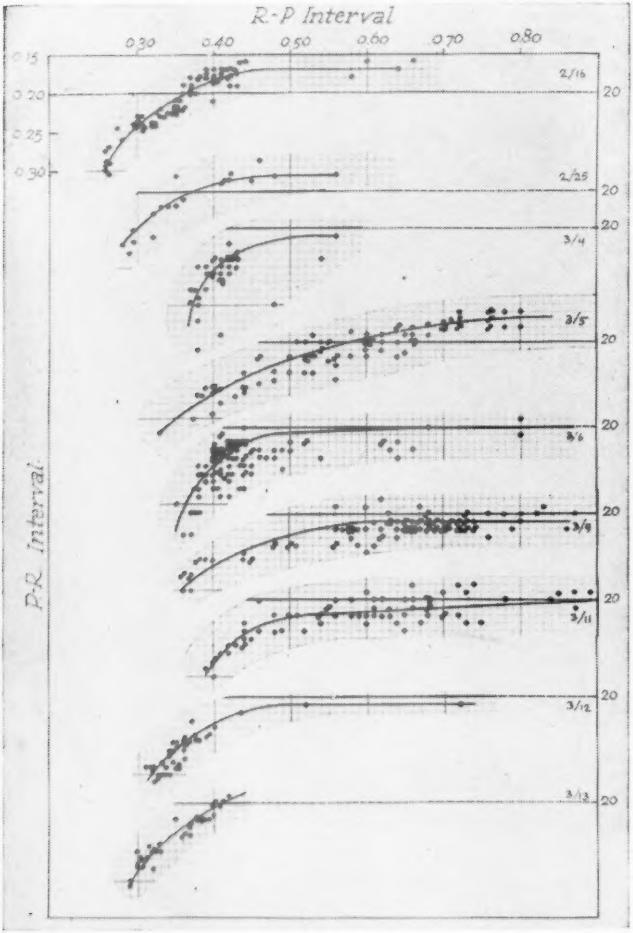


Figure 11. Recovery curves for forward conduction as affected by digitalis. The dates are shown on the right border; for the corresponding level of digitalization, compare with Figure 10.

The recovery curves obtained by graphically relating the R-P and the accompanying P-R intervals are shown in Fig. 11. Delay of recovery is apparent, being most

marked on those days on which retrograde conduction was also conspiculously delayed. Parallel to the sharp drop in the latter, there was a marked acceleration of re-

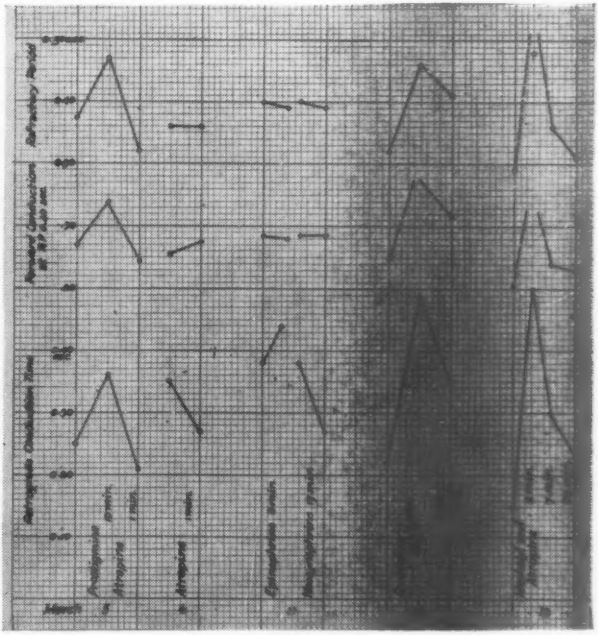


Figure 12. The effect of drugs on properties of the A-V node. In each instance the control value is charted; the drug was given and after the lapse of time as indicated the test curve was begun. For further details see text.

covery, suggesting that the two properties are closely related. The forward conduction times after recovery was effected, as criteria of completeness of recovery, show in general some prolongation due to digitalis, but these were not consistent.

Vagal stimulation via carotid sinus pressure was not feasible for the relatively long periods of time necessary to obtain curves suitable for comparison. When employed for short periods, however, we did note that complexes with retrograde conduction times so long that reciprocation should have been anticipated, failed to return to the ventricle. This

indicates a prolongation of nodal refractoriness under vagal influence. The strips obtained are insufficient for other deductions, and our conclusions concerning the vagus effect

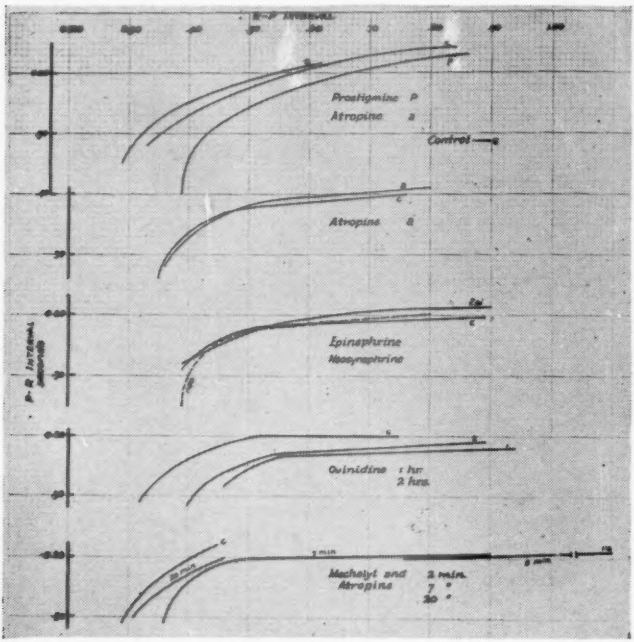


Figure 13. Recovery curves of the A-V node as affected by the drugs employed. For purposes of comparison only the smooth curves are shown; the individual points as shown in Figure 11 are omitted here.

are chiefly derived from observations made after the injection of cholinergic drugs.

Prostigmine was injected intramuscularly in the dosage of 1 mgm. Observations made 10 minutes later indicated (Fig. 12) delay in both retrograde and forward conduction, and prolongation of the refractory period. Recovery (Fig. 13) was incomplete and much delayed; the curve resembles that obtained by Lewis and Master (1925-26) after vagal stimulation.

Mecholyl (acetyl-B-methyl choline) showed an essentially similar effect, with marked changes following it.

These are perhaps not the full effect, since immediately after the injection of 20 mgm. subcutaneously the patient experienced a severe reaction which necessitated the immediate intravenous administration of atropine. Curves taken as soon as possible showed the marked delay in retrograde conduction. The refractory period could not be accurately determined, since all complexes with an R-P interval of less than 0.48 sec. failed to show reciprocation, and all above 0.76 sec. showed it; there were none showing intermediate values. The refractory period therefore lies somewhere in this range. Forward conduction could not be measured as usual at this time, since there were no R-P intervals of 0.40 sec. which showed reciprocal beats. The effects on recovery, as well as those on the other properties measured, must be judged in part by their disappearance under the influence of atropine, as this gradually became manifest.

Quinidine produced clear cut depressant effects on the nodal tissues, prolonging refractoriness, delaying both retrograde and forward conduction, and delaying recovery and rendering it incomplete. The data for quinidine are shown in detail in Fig. 9, and the recovery curves are charted in Fig. 13. This effect was produced by 5 grains given by mouth. Most marked at one hour, the effect had partially receded at two hours.

Atropine alone given intravenously in a 1/50 grain dose, produced little effect on the refractory period or on forward conduction. Retrograde conduction was definitely accelerated however. When atropine was given after prostigmine and mecholyl, the depressant effects of the cholinergic drugs were rapidly neutralized, and in the case of its use after prostigmine, actual acceleration of conduction and shortening of refractoriness and recovery were observed.

Epinephrine (0.5 cc. subcutaneously) produced no significant effect on refractoriness or forward conduction. The mean retrograde conduction time however was increased from 0.38 sec. to 0.44 sec. The recovery curve was distinctly changed, with recovery slower but finally more complete.

Neosynephrine (5 mgm. subcutaneously) also showed little significant effect on refractoriness or forward conduction, nor did it significantly influence the curve of recovery. There was however a distinct acceleration of mean retrograde conduction from 0.38 sec. to 0.27 sec.

The time intervals after dosage are indicated in Fig 12. It is to be remembered that this is the time at the beginning of the electrocardiogram, and that from 6 to 10 minutes were required for its completion. The observations cover this period of time. Additional curves were taken in several instances, but added no further information and hence are omitted.

DISCUSSION

The state of the heart muscle must certainly largely influence the result produced by drug administration. This is exemplified by the striking effects of atropine when given after mecholyl or prostigmine, as compared to its minimal effect when given alone. It must be borne in mind too that the effects described above are results of drugs administered to a heart digitalized to a varying degree. This circumstance was due to clinical factors which we could not control, and disappearance of the reciprocal mechanism prevented repetition.

Separation of the effect of digitalis into a vagal and direct muscular action has long been customary; the direct muscular effect is now recognized as predominant. It is evident that as far as its effects on the A-V nodal tissue are concerned, digitalis acts like cholinergic drugs, with the exception of its early effect on retrograde conduction. Of all the digitalis effects, the latter was the only one influenced by atropine, which indicates that the direct muscular action of the glocoside was more important than any indirect vagal effect. The action on retrograde conduction resembles the effect noted by Clark and Mines (1914) on forward conduction in the frog heart. It is obvious that reciprocation will be most frequent when R-P intervals are prolonged relatively more than is the refractory period to forward conduction.

Our results certainly justify the conclusion that vagus stimulation and cholinergic drugs depress the A-V nodal tissues, prolonging refractoriness, delaying conduction and

rendering recovery slow and sometimes incomplete. These data on refractoriness do not agree with the results obtained in dogs by Lewis, Drury and Iliescu (1921), but ours seem more consistent with the undisputed effects on conduction. We cannot, of course, divorce changes of conduction from our measurements of refractoriness. Hence, unless it be granted that the junctional tissues react in a fashion fundamentally different from that of auricular or ventricular muscle, we must take refuge in Lewis' concept of an "effective" refractory period in order to reconcile our findings with recent work on muscle refractoriness after digitalis and quinidine. Both of these drugs act on the A-V node like the vagomimetic group, though the latter is known to paralyze the vagus endings. It is apparent then that the effects are direct ones on the muscle cells, with depression of all properties studied with the possible exception of retrograde conduction.

Vagal paralysis, and sympathetic stimulation, seemed relatively ineffective. Unless the vagus was previously strongly stimulated, atropine definitely affected only retrograde conduction. This same result was noted after the administration of epinephrine and neosynephrine, retrograde conduction being delayed by the former and accelerated by the latter. These single observations may not be significant, but in order to explain them one must assume a paradoxical vagal stimulation in the case of the epinephrine effect. This finding does not agree with those of Danielopolu and Proca (1926). In contrast, the vagus is known to be stimulated by neosynephrine but in this case the opposite effect was obtained. A clear understanding of these findings must remain in doubt. We have noted with interest the fact that retrograde conduction seems far more susceptible to change than conduction in the normal forward direction.

We do not feel that changes in nodal rate play any part in explaining the observed changes in refractoriness. With one exception, the changes in rate were minimal (Cf. Table I). More important is the fact that changes in rate in this range produce relatively little change in the refractory period. We were able to confirm this by measurements of the Q-T interval in our tracings, though of

course this pertained to the ventricular muscle, rather than to the A-V node.

TABLE 1

	Rate per Minute	Refractory period sec.	Forward Conduction	Retrograde Conduction
Control	48	0.375	0.27	0.25
Prostigmine	48	.47	.34	.36
Atropine	53	.32	.245	.21
Control	50	.36	.255	.35
Atropine	50	.36	.275	.27
Control	48	.40	.285	.38
Epinephrine	50	.39	.28	.44
Neosynephrine	47	.39	.285	.27
Control	52	.32	.25	.22
Quinidine	46	.46	—	.49
	44	.41	.315	.35
Control	51	.29	.205	.15
Mecholyl and	33	.48-.76	—	.50
atropine	50	.36	.24	.30
	52	.31	.23	.23

We noted that triplets were most common on those days on which retrograde conduction was most prolonged. In addition, those drugs which delayed retrograde conduction, particularly mecholyl, seemed to increase the frequency of triplets. This fact might have been anticipated from the experimental procedures used by Scherf, but we suspect that the other properties of the nodal tissue play a part, which we were unable to identify, in determining the frequency of triplets.

SUMMARY

We have reported three cases of reciprocal rhythm. One case has been carefully studied electrocardiographically, and the detailed findings have led us to propose a precise concept of the physiological processes in operation. Drugs, known to affect the heart, have been administered, and their effects observed on refractoriness, conduction, and recovery of the A-V nodal tissues.

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CALLING ATTENTION TO:

ITEMS OF POSSIBLE INTEREST TO FRIENDS OF OUR EFFORT

AUGUST, 1943

1. **Texas Reports on Biology & Medicine:** 2nd issue, with articles on spotted fever, vasomotor factors in the etiology of hypertension, and vitamins on adaptation to low pressure, may be a wee bit delayed. Tropical disturbances of moderate intensity do peculiar things. 3rd issue coming up has articles on war surgery, neurosyphilis, and rickettsial diseases. May there be no more hurricanes here for a spell!

2. **For the historically minded:** Random House, New York, issues G. Myers' **History of Bigotry in the United States,** a timely study in nasty psychology. P. B. Hoeber, New York, publishes A. E. Truby's pleasant **Memoir of Walter Reed: The Yellow Fever Episode.** A beautifully illustrated series of articles on Vesalius by Castiglioni, Francis, and Fisch, gets noticed in **Time (Bull. Med. Lib. Asso.,** 31: 201-259, July, 1943).

3. **Books, Books, Books:** It's time to parody Kipling! W. B. Doherty & D. D. Runes' **Rehabilitation of the War Injured** (Philosophical Library, New York,—sic!) looks like the same outfit's **War Medicine,**— a bound collection of recent reprints. W. D. Forbus writes a new style pathology: **Reaction to Injury,** issued by Williams & Wilkins, Baltimore. A. E. Wright discusses the **Pathology & Treatment of War Wounds** (Wm. Heineman, London). Same publisher issues D. Harley's **Blood Group Determination.** Academic Press, New York, offers first volume of R. S. Harris & K. V. Thimann's **Vitamins & Hormones.** S. Wolf & H. G. Wolff (yes) long study **Human Gastric Function** in the style of Wm. Beaumont (Oxford Press, N. Y.). Grune & Stratton, N. Y., offer a $12.00 book by E. Urbach on **Allergy.** The Commonwealth Fund, N. Y., issues a neat brochure by G. N. Papanicolaou & H. F. Traut on **Diagnosis of Uterine Cancer by the Vaginal Smear.** Volume 6, Annals American Academy of Political & Social Science is on **Nutrition and Food Supply: The War and After.**

4. **Hot Session Faraday Society:** Important discussion on modes of drug action is announced by Faraday Society for Friday, September 24, 1943, at the Hotel Rembrant, South Kensington, London, SW 7, with H. H. Dale & J. H. Gaddum opening the AM meeting with Quastel & McIlwain on biological aspects, & E. K. Rideal opening the PM meeting on physical chemical aspects, with King, Schulman & Scott.

5. **Here's to Edwards Bros. lithoprinting:** Alien Property Custodian releases lithoprinted German scientific periodicals from Edwards Bros., Ann Arbor, with flashy orange covers. H. Lettre & H. Fernholz report on relation between toxic mitosis effects & constitution of colchicine derivatives, showing significance of sympathicomimetic group **(Hoppe-Seyler's Ztschr. Physiol. Chem.,** 278: 175, 1943). H. Albers & Co., give much data on hemolytic action of acids & bases **(Biochem. Ztschr.,** 314: 186, '43).

6. **Etc.:** H. Henry & M. Stacey (Birmingham) study histochemistry of Gram staining & suggest Gram-positive (dye-retaining) mate-

rial is high molecular complex of a reduced basic protein substrate with magnesium ribonucleate (**Nature**: 151: 671, June 12, '43). J. Boyes-Watson & M. F. Perntz find by X-ray analysis of hemoglobin that the molecule is a rigid four-layered platelet 36 x 64 x 48 A° in size (**ibid**, June 26, p. 714). K. Bailey & Co. show same peculiar shape of molecule common to keratin, myosin, fibrinogin & fibrin & suggest biochemical adaptive evolution (**ibid.**, p. 716). F. Sjostrand (Stockholm) describes technique for electron microscopic examination of tissues (**ibid.**, p. 725). G. S. Carter & Co. (**ibid.**, p. 728) find paraxanthine is normal antithyroid, & metabolism is low if concentration is balanced with thyroid, & high if either are in excess. O. A. Trowell (**ibid.**, p. 730) reports that anoxemia causes liver vacuoles. K. Meyer et al. (N. Y.) by-pass rapid excretion of penicillin in noting effectiveness of slow hydrolyzing ethyl & butyl esters (**Proc. Soc. Exp. Biol. Med.**, 53: 100, '43). S. Rothman & P. Flesch (**ibid.**, p. 134) isolate red iron pigment from human red-heads,—no wonder they're tough! T. Gillman (**S. Afr. J. Med. Sci.**, 8: 50, '43) recommends excretion of neutral red by gastric mucosa (max. conc. 6-20 minutes after IV inj. 5cc. 1% sol.) as a valuable test of gastric function.

SEPTEMBER, 1943

1. **Special Issues**: Congratulations to Benno Schwabe & Co., Basle, for the special chemotherapy number (19/20) **Schweizerische Medizinische Wochenschrift**, 1943, dedicated to the International Committee of the Red Cross. Pages 549 to 685 deal mostly with sulfonamide derivatives in various clinical conditions, with general discussion by R. Stachelin, H. Staub, M. Hartmann & R. Meier on basic principles, and bibliography of 958 articles by O. Merkelbach. Interesting how little United Nations scientific or medical publications have reached Switzerland since 1942. But even the University of Basle offers special courses in tropical medicine. To be noted are F. Verzar's **Theorie der Muskelkontraktion**, and A. L. Vischer's **Das Alter als Schicksal und Erfullung**,—also the new **Helvetica Physiologica et Pharmacologica Acta**, quarterly at Fr. 31.50, if you can get it! The June 1943 issue **Bulletin of the American College of Surgeons** (28: 90-239) is all war, from care of the injured to a selected bibliography. The July issue of **California & Western Medicine** has a tuberculosis supplement (59: 25-71, 1943) which deserves wide circulation, reprinting, and a lot more rayrah,—most of the notes warrant extension and republishing.

2. **And more books**: C. C. Thomas (now in Frank Lloyd Wright's Springfield, Ill., house) announces I. H. Page's **Hypertension**,—a manual for patients, and C. C. Higgins' **Renal Lithiasis. New & Non Official Remedies** (AMA, Chicago, 1943 issue) continues to show improvement in organization & material. Williams & Wilkins (Balt.) issue B. Ratner's **Allergy, Anaphylaxis, Immunotherapy**. MacMillan (N. Y. 11) offer W. K. Livingston's **Pain Mechanisms: A Physiological Interpretation of Causalgia**. P. B. Hoeber has another W. C. Alvarez on **Nervousness, Indigestion & Pain**, & has ready a big **Clinical Tropical Medicine** edited by A. T. Bercovitz. Finally there appear both volumes of the important **Pharmacology of the Opium Alkaloids**, by H. Krue-

ger, N. B. Eddy & M. Sumwalt (Suppl. 165, **Pub. Health Rep.**, Washington) with a whopping bibliography of over 10,000 items! American council of Public Affairs, Washington, issues S. Wilson's **Food & Drug Regulation.** Symposium of Association for Research in Nervous & Mental Diseases on **Role of Nutritional Deficiency in Nervous & Mental Diseases** is published by Williams & Wilkins. And we've just received the same outfit's **Antigonadotropic Factor with Consideration of the Antihormone Problem** by B. Zondek & F. Sulman. Also note **Cytology & Cell Physiology**, edited by G. Bourne, & including sections by J. F. Danielli & H. Blaschko, offered by Oxford Press at 20s. C. C. Thomas published **Medical Progress Annuals** covering series of articles appearing in New England Journal of Medicine.

3. **Interesting:** J. Davidson finds body louse eggs develop 25% per day at body heat (**Med. J. Austral.**, 1: 533, June 12, 1943). R. H. Williams & G. W. Bissell confirm E. B. Astwood's finding (**JAMA**, 122: 78, 1943) that thiouracil successfully controls thyrotoxicosis in doses of 0.2 gm. per 4 hours, giving blood concentration of 3 mgm. per 100 c., & 300 mgm. per day in urine (**Science**, 98: 156, Aug 13, 1943. F. R. Winton & Co. report renal damage after crush injury to limbs (**Quart. J. Exp. Physiol.**, 32: 89, 1943). M. C. Sanz (Bern) in studies on brain metabolism finds no acetylcholine production in absence of glucose & increase in metabolism with HCN (**Pfluger's Arch. ges. Physiol.**, 246, 597, 1943). G. Domini & H. Rein (**ibid.**, p. 608) confirm our old report that lactate ions dilate peripheral vessels independently of pH (**Am. J. Physiol.**, 80: 107, 1926). H. Kwiatowski (**J. Physiol.**, 102: 32, 1943) finds much histamine in distal parts of sensory nerves, none in central nervous system or motor nerves, proposes histaminergic nerves. B. C. Bose & B. Mukerji discuss physiologically active fractions of Indian hemp (**Nature**, 152: 109, July 24, 1943). In July **Physiological Reviews** are articles by E. F. Hirsch & S. Weinhouse on lipids in atherosclerosis, L. Pauling & Co. on antigens, antibodies & precipitation reaction, F. A. Hellebrandt on verticle stance of man.

4. **Ave! Helvetica Physiologica et Pharmakologica Acta**, O. A. M. Wyss, Geneva, Editor. 1st issue contains articles by S. Burgi on tegmental reaction, A. Fleisch on vitamin A, W. R. Hess on subcortical centers, W. Bloch on relation of hypothalamus to resp. metab., W. Shuler on relation between age of metabolism, & proceedings Jan. 30 meeting of the Swiss Society for Physiology & Pharmacology.

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BACTERIOSTATIC PROPERTIES OF SULFANILAMIDE AND SOME OF ITS DERIVATIVES:

*II. Phthalylsulfathiazole, A New Chemotherapeutic Agent Locally Active in the Gastroenteric Tract**

EDGAR J. POTH AND CHARLES A. ROSS

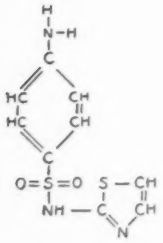
In 1941 Poth and Knotts announced the discovery of a series of acylated sulfonamides, including succinylsulfathiazole, which is only sparingly absorbed from the gastrointestinal tract and shows a marked local bacteriostatic activity. A subsequent report by Poth, Knotts, Lee and Inui detailed the observations on fifteen sulfanilamide derivatives as to their local bacteriostatic activity in the gastrointestinal tract followed by various reports on the clinical use of succinylsulfathiazole. A toxicological study of succinylsulfathiazole was reported upon by Welch, Mattis and Latven in July, 1942. These studies have been extended to an additional nineteen derivatives of sulfanilamide and chemically related compounds† for their local bacteriostatic activity, and the results of these studies will be the basis of this report. Of these compounds, twelve are N^4-acyl derivatives of sulfonamides which were synthesized according to the general procedure of Miller, Rock and Moore, and Moore and Miller.

In a continued search for an ideal intestinal antiseptic, that is, one which is sparingly absorbed from the gastrointestinal tract and possesses strong antibacterial action locally, another sulfonamide, phthalylsulfathiazole, which approximates these specifications, has been found (Poth and Ross, 1943). A comparison of the structural formulae of this compound and succinylsulfathiazole (Sulfasuxidine) shows their chemical relationship. (See formulae, p. 346.) Phthalic acid, however, is a dibasic acid aromatic compound while succinic acid is a dibasic aliphatic compound, and it would not be unlikely that the condensation products of these two acids with sulfathiazole should have considerably different chemical and physical properties as

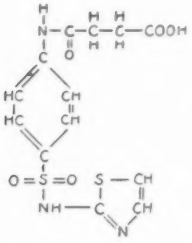
* From the Department of Surgery, Johns Hopkins University School of Medicine, and the Department of Surgery, The University of Texas Medical Branch, Galveston. Submitted for publication August 9, 1943. This work was aided by a grant from Sharp & Dohme, Inc., Philadelphia.

† These compounds were synthesized and supplied by Sharp & Dohme, Inc., of Philadelphia, Pennsylvania.

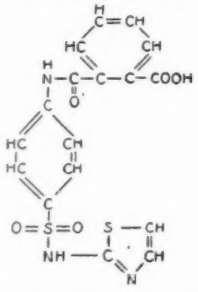
well as a divergence in their pharmacodynamic action. Phthalylsulfathiazole is practically insoluble in water and is a weak acid. The finely divided powder suspended in an aqueous sodium bicarbonate solution will liberate carbon dioxide slowly at room temperature. The sodium salt of phthalylsulfathiazole is moderately soluble. A 20 per cent aqueous solution of the salt can be prepared if a 10 per cent excess of sodium hydroxide is used. The sodium salt can be recovered from this solution by chilling in an ice bath, and it can be further purified by recrystal-



Sulfathiazole



Succinylsulfathiazole
'Sulfasuxidine'



*Phthalylsulfathiazole**
'Sulfathalidine'

lization from water buffered to pH 7. Care should be taken not to warm the solution above 50° C. because of the tendency of this compound to hydrolyze. Studies on the rate of hydrolysis in acid and alkaline solutions are presented in Chart 8, which shows that the rate of hydrolysis in aqueous solution is slowest in the neighborhood of pH 7. The following information is furnished by Miller: The sodium salt, recrystallized from water, washed with several large portions of acetone, and dried in an oven at 50°-60° C., has the following characteristics: Melting point, 98-99° C., effervesces at 110-115° C.; becomes solid again at 180° C.; and finally decomposes between 210-220° C. A sample dried for two days at 60° C. analyzed as follows:

	*Calculated**	*Found*
Nitrogen	8.15	8.10 - 8.11
Sodium	4.46	4.06 - 4.16

*Calculated for five moles of water of crystallization.

*N4—Phthalylsulfathiazole is registered under the proprietary designation of "Sulfathalidine" by Sharp & Dohme, Inc., Philadelphia.

The salt dried in the Abdenholder apparatus showed a weight loss corresponding to 4.61 molecules of water.

Analysis of this sample:

	Calculated	*Found*
Nitrogen	9.88	9.88 - 9.91

A one millimolar solution of the sodium salt in conductivity water gave a pH reading of 5.59 at 26° C. (Note: It should be anticipated that an aqueous solution of the sodium salt would be alkaline rather than acid, but repeated determinations on different samples of the sodium salt consistently showed the aqueous solutions to have a slightly acid reaction, as indicated by the pH reading of 5.59 at 26° C.)

Methods of Investigation

Since this study was undertaken to find compounds with suitable properties for therapeutic use as intestinal antiseptics, any drug which gave indications of having toxic properties was discarded without further investigation. It has been found that anorexia is an early sign of toxicity in the dog.

Dogs were used exclusively in these feeding experiments. An initial stool specimen was taken directly from the rectum after food had been withheld for twenty-four hours or after the animal had received his standardized meat ration for a minimum of twenty-four hours. The meat ration consisted of boiled beef lungs which were ground finely and mixed with a small quantity of rendered beef tallow to bind the meat together so that it could be made into suitable balls for feeding by an automatic device. Ordinarily, the drug under study is mixed with the meat ration which is then divided into six equal portions. The animal receives a feeding every four hours day and night. The animals are kept somewhat hungry to ensure their consumption of the food and the contained drug immediately upon its delivery.

Initial studies were conducted on all drugs at a daily dosage level of 1.0 and 0.5 grams per kilo divided into six four-hour doses. In the event a compound gave evidence of good bacteriostatic properties, its efficacy was further studied at dosages of 0.25, 0.1, and 0.05 grams per

kilogram of body weight thereby determining the smallest effective dose and indicating the therapeutic ratio.

Quantitative Chemical Estimation of the Compounds

The quantitative determination of the drugs in the blood, urine, and feces followed the method outlined by Bratton and Marshall. In each instance it was necessary to establish the definitive procedure, because the optimum conditions for hydrolysis of the different compounds varies considerably. For example, succinylsulfathiazole must be heated in 0.8 N HCl for two hours on a boiling water bath for quantitative hydrolysis while phthalylsulfathiazole requires that it be similarly heated for the same length of time in 0.2 N HCl as follows:

Determination in Blood:

Add 0.1 cc. of blood to 9.5 cc. of a solution containing 1 gm. of saponin per liter. Precipitate the proteins with 2.4 cc. of 15% trichloracetic acid. Allow to flocculate and filter. This filtered solution will be known as the filtrate.

To determine the free or deacylated compound:

To 4 cc. of the filtrate add 1.2 cc. of trichloracetic acid and 4.8 cc. of water.

To develop the color:

Add 1 cc. of 0.1% $NaNO_2$ solution. Mix, wait for 3 min., add 1 cc. of 0.5% ammonium sulfamate solution. Mix, wait for 2 min., add 1 cc. of 0.1% N-(1-naphthyl)ethylenediamine dihydrochloride, mix and read in the colorimeter. The dilution factor will be 300.

To determine the total or combined free and conjugated compound:

To 4 cc. of the filtrate add 0.5 cc. of 4 N HCl plus approximately 5.5 cc. of distilled water, and heat on a boiling water bath for 2 hours. This is best carried out in a Pyrex test tube measuring 16x150 mm. and calibrated to 10 cc. Care should be taken during the heating process to maintain the level at approximately 10 cc. Finally cool and make up the volume of 10 cc. with water.

Develop the color reagent as above and read in the colorimeter. The dilution factor will be 300.

Urine:

Dilute 1 cc. of urine to 100 cc. with water.

To determine the free or deacylated compound:

To 1 cc. of the diluted urine add 7 cc. of water and 2 cc. of 15% trichloracetic acid.

Develop the color reagent as above and read in the colorimeter. The dilution factor will be 1000.

To determine the total or combined free and conjugated compound.

To 1 cc. of the diluted urine add approximately 8.5 cc. of distilled water and 0.5 cc. of 4 N HCl. Heat on a boiling water bath for 2 hours, maintaining the volume at approximately 10 cc. Cool, make up the volume to 10 cc., and develop the color as above, and read in a colorimeter. The dilution factor will be 1000.

An Evelyn colorimeter was employed. The determinations were carried out on freshly drawn blood specimens, catheterized urine specimens, and feces taken directly from the rectum. Specimens were collected about two hours after the administration of a dose of drug.

Routine Bactriologic Studies

Fecal specimens were taken directly from the rectum, and dilutions made immediately for culture or the specimens were chilled and kept at refrigerator temperatures until cultured. Quantitative dilutions were made in two ways. Either a suspension was centrifuged at 1700 revolutions per minute and the quantity of sediment estimated in a graduated tube, one cubic centimeter of the sediment being taken as one gram of stool, or a 1-to-100 suspension was made by suspending stool in 0.9% NaCl solution and adjusted by adding more solution or stool as required to bring the turbidity up to a standardized level. The lactose fermenting coliform organisms were counted on pour plates using desoxycholate agar, and total aerobic counts were made using plain infusion agar plates. The differential alteration of aerobic Gram negative and Gram positive organisms was followed by serial dilutions of stool suspensions in an infusion broth. After incubation for 48 hours the highest dilutions in which these two groups of organisms grew out was determined by Gram staining. The serial dilution technique will ordinarily show organisms to be present in the next higher dilution as when observed by the pour plate methods. Anaerobic counts were determined by heating the prepared stool suspensions in a water bath for ten minutes at 80° C. to destroy the vegetative forms. Serial dilutions of the suspension, made in sterile 0.9% NaCl solution, were made by pipetting 1 cc.

of each dilution into the bottom of tubes containing a 0.3% dextrose, semisolid, infusion agar medium. Gas formation and visual evidence of growth after incubation for 48 hours in an anaerobic jar indicated the highest dilution containing spores.

All media contained 5 mgm. per cent of p-aminobenzoic acid to inhibit the action of the sulfonamides.

Relative Bacteriostatic Activity of Various N^4-Acyl Derivatives of Sulfonamides

In Table 1 is listed a number of sulfonamides showing their relative local bacteriostatic action in the gastro-intestinal tract of the dog as indicated by the alteration of the coliform bacteria. The concentrations of both the free and conjugated forms of the drugs are given in the blood and urine for those substances which showed any promise of being useful drugs. Succinylsulfanilamide and succinylsulfathiazole have been reported previously and are included here for comparison. Four of the new compounds included in this table show relatively good bacteriostatic action. These are maleylsulfathiazole, quinolinylsulfathiazole, phthalylsulfathiazole, and succinylsulfanilylsulfanilamide. The succinylsulfanilylsulfanilamide, while quite active, showed a relatively high degree of toxicity. Quinolinylsulfathiazole is a promising compound showing about the same activity as succinylsulfathiazole. It was not studied beyond preliminary observations because of the prohibitive cost of the intermediates. Maleylsulfathiazole gives excellent local bacteriostatic action without immediate evidence of toxicity. The rapid rate of hydrolysis of the compound, however, apparently gives rise to relatively high concentrations of the free sulfathiazole in the blood and urine. In this connection, it should be realized that the high percentage of the free form of the drug might be due to the fact that it is split, not in the body, but rather during the chemical determination of the drug. While maleylsulfathiazole shows relatively good bacteriostasis, it is less active than phthalylsulfathiazole. This latter compound is the most promising of the entire group. It has high bacteriostatic action and has not caused toxic manifestations when administered orally in therapeutic doses.

TABLE 1. Comparison of the Absorption, Excretion and Toxicity and Bacteriostatic Activity of the N4 Acyl Derivatives of Sulfonamides, as Indicated by the Local Effects on the Coliform Bacteria in the Bowel of the Dog.

Drug	Total Daily Dose Divided into 6 Daily Doses—Grms. per kilo	Number of Animals Tested	Maximum Concentration of Conjugated Drug in Blood Mgm.%	Maximum Concentration of Conjugated Drug in Urine Mgm.%	Comparative Antibacterial Action Against B. coli	Relative Toxicity
Sulfanilylguanidine	0.3	10	5.0#	—	++	0
	1.0	15	15.0#	Crystals #	++	+++
	5.0	10	35.0#	Crystals #	++	++++
Succinylsulfanilamide	0.1	1	—	—		0
	0.25	8	1.6	960	0	0
	0.50	8	1.0	—	+	0
	1.0	8	1.5	2400	++	0
	2.0	1	1.5	—	++++	
	5.0	1	1.5	—	++++	++
Succinylsulfathiazole	0.05	2	4.0	170	+	0
	0.10	6	5.0	270	++	0
	0.25	5	4.0	560	++	0
	0.5	12	4.0	600	+++	0
	1.0	24	5.0	600	++++	0
	2.0	9	7.0	600	++++	+
	5.0	3	—	—	++++	++
Oxalylsulfathiazole	0.5	1	—	—	±	++
	1.0	1	—	—	±	+++
Malonylsulfathiazole	0.5	1	—	—	0	++
	1.0	1	—	—	0	+++
Maleylsulfathiazole	0.05	1	1.5*	170*	0	0
	0.10	1	1.9*	216*	±	0
	0.25	1	4.9	330*	++	0
	0.50	1	4.4*	430*	+++	0
	1.0	1	10.9*	909*	++++	0
Quinolinylsulfathiazole	0.031	1	0	13.	0	0
	0.063	1	0	89.	0	0
	0.125	1	1.3	96.	0	0
	1.0	1	—	—	++++	0
Phthalylsulfathiazole	0.05	1	2.3	40	±	0
	0.10	3	1.8	41	++	0
	0.25	7	2.7	310	+++	0
	0.50	10	2.7	308	++++	0
	1.0	4	3.3	1560	++++	0
Succinylsulfanilylsulfanilamide	0.1	2	3.0	99	+	0
	0.25	1	3.0	150	+	0±
	0.50	2	4.0	300	++	+
	1.0	2	6.8	400	+++	++
Succinylsulfanilylsulfathiazole	0.5	1	—	—	0	0
	1.0	1	—	—		0
Sulfa-4-oxy-6-methyl pyrimidine	1.0	1	—	—	±	++
Phthalylsulfanilamide	0.125	1	—	50	0	0
	0.25	1	—	100	0	0
	0.5	2	1.0	250	±	0
	1.0	1	2.0	300	±	0
Phthalylsulfamerazine	0.25	1	—	100	0	0
	0.5	2	—	—	0	0
	1.0	1	—	200	0	0
Phthalylsulfadiazine	0.25	1	—	225	0	0
	0.5	2	—	—	0	0
	1.0	1	—	—	±	0
o-methylsuccinylmetanilamide	0.5	1	0.5	300	0	0
	1.0	1	0.9	600	0	0

* Free form. Maleysulfathiazole is readily hydrolyzed and appears to be extensively split up by the body.
# Free form of drug—not conjugated.

Local Antibacterial Activity of Phthalylsulfathiazole in the Gastrointestinal Tract

Table 2 indicates that phthalylsulfathiazole has from two to four times greater bacteriostatic activity than succinylsulfathiazole, as indicated by the effect on coliform

TABLE 2. A Comparison between Phthalylsulfathiazole and Succinylsulfathiazole when administered orally.

DRUG	Dose gm/kilo/ day	Drug Con. in Blood Mgm. per 100 cc.		Drug Conc. in Urine Mgm. per 100 cc.		Relative Bacterio-stasis
		Free	Conjugated	Free	Conjugated	
Phthalyl-sulfathiazole	1.0	3.0	3.0	—	—	++++
Succinyl-sulfathiazole	1.0	3.5	5.0	360	600	++++
Phthalyl-sulfathiazole	0.5	2.3	2.7	174	210	++++
Succinyl-sulfathiazole	0.5	3.5	4.0	180	600	+++
Phthalylsulfa-thiazole	0.25	1.5	2.4	180	200	+++
Succinylsulfa-thiazole	0.25	4.0	4.0	125	560	++

organisms in the gastroenteric tract of the dog. When phthalylsulfathiazole is administered orally at regular hour intervals to animals on a straight meat diet, there is an alteration of the coliform flora as given in Chart 1. A dose as small as 0.125 grams per kilo of body weight per day, causes a significant lowering in the coliform population. Doses of 0.25 grams or more per kilo of body weight, administered in a similar manner, cause more profound and more rapid alterations in the bacterial counts. With doses of 0.25 grams per kilo or more, frequently no coliform organisms grow out after the third day of administration. It has been noticed also when phthalylsulfathiazole is administered by other than the oral route so as to maintain a high tissue concentration, that the drug is excreted into the bowel to give concentrations of the drug in the feces which result in inhibition of the coliform organisms. This alteration is somewhat more de-

layed than when the drug is administered by mouth, although it may frequently be of the same order of magnitude. Animals have been fed the drug for as long as thirty-five days during which time the marked suppression of the coliform flora has been maintained.

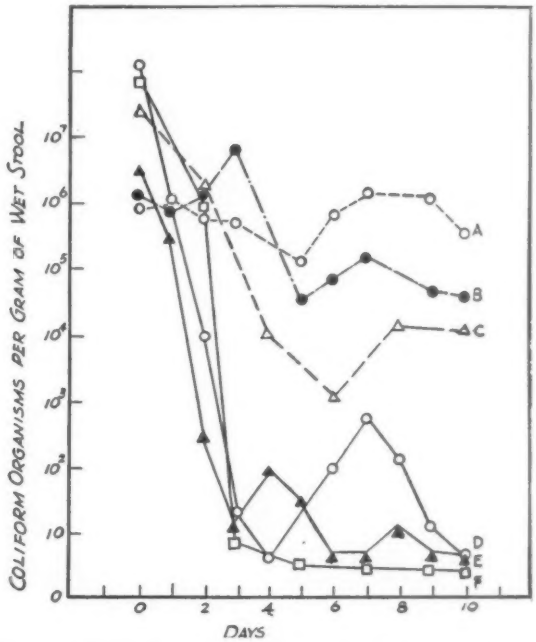


Chart 1. A demonstration of the alteration of the bacterial flora of the bowel of the dog following the oral administration of various dosages of phthalylsulfathiazole as reflected by the change in the number of coliform organisms in the rectal feces. The total daily dose was mixed with ground meat, divided into six portions, and one of these portions fed every four hours day and night. These are representative curves of individual experiments: A. 0.05 grams per kilo; B. 0.10 grams per kilo; C. 0.125 grams per kilo; D. 0.25 grams per kilo; E. 0.50 grams per kilo; and F. 1.0 grams per kilo.

The Absorption and Excretion of Phthalylsulfathiazole

The absorption and excretion of this drug by the dog have been investigated following its administration orally, intravenously, intraperitoneally, and subcutaneously. Following oral administration, the compound is but sparingly absorbed, as is indicated in Tables 1 and 2, and Chart 2. As is indicated in Table 1, the concentration of the conjugated drug in the blood is little influenced by the quan-

tity of the oral dose. The maximum concentration of the conjugated drug in the blood with a dose of 1.0 gram per kilo per day in six divided doses has not exceeded 3.3 mgm. per 100 cc. While it is not convenient to determine quantitative total urinary output of the drug, because of possible fecal contamination, the concentration of the conjugation compound in the urine indicates that somewhat greater quantities of drug are absorbed from the gastrointestinal tract with increasing doses. Chart 2 gives the relative concentrations of the free and conjugated drugs

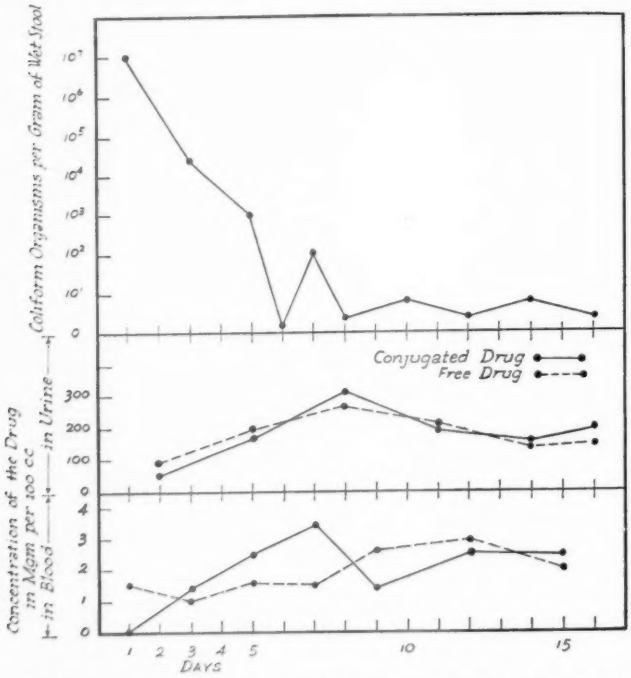


Chart 2. An illustration of the correlation between the bacteriostatic action of phthalylsulfathiazole, when administered to the dog orally at a dosage of 0.5 grams per kilo of body weight daily divided into six equal portions and given at four-hour intervals day and night, and the concentrations of the drugs in the blood and urine. The extent to which phthalylsulfathiazole is hydrolyzed in the body is indicated by the relative concentrations of the conjugated and free forms of the sulfonamide.

in the blood and urine of a dog receiving 0.5 gram per kilo of body weight daily, divided into six equal portions and administered orally at four-hour intervals, day and

night. Although animals have been maintained on the drug for long periods of time, there has been no indication of interference with urinary excretion, nor has there been any increase in the concentration of the drug in the blood.

Following the intravenous administration of one gram per kilo of body weight of the sodium salt of phthalylsul-

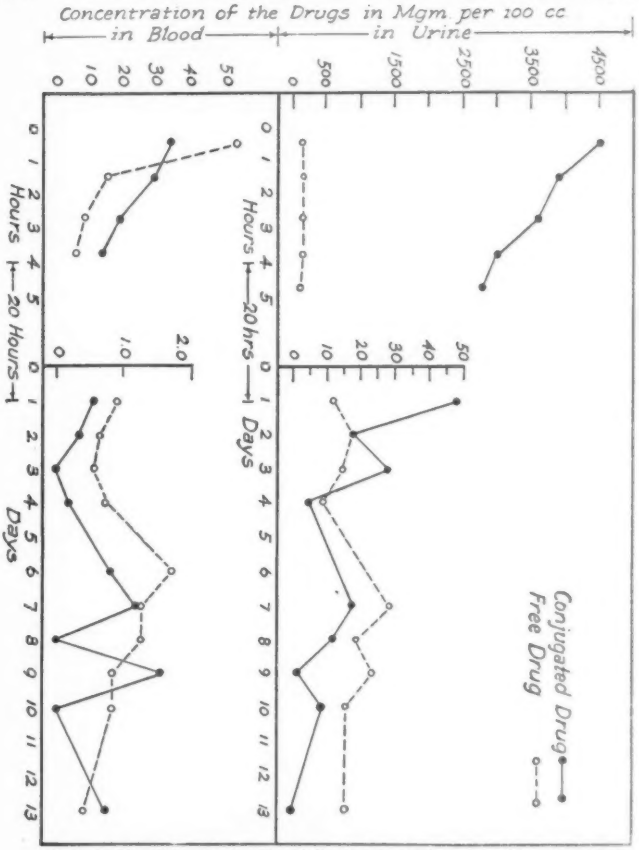


Chart 3. The Rate of Excretion following the intravenous injection of 1.0 gram per kilo of body weight daily of phthalylsulfathiazole in the form of the sodium salt in 10 per cent aqueous solution. After the initial five-hour period the specimens were taken just before administration of the daily injection.

fathiazole, the drug is rapidly eliminated, as is indicated in Chart 3. If it is assumed that the blood volume in liters is equal to one-tenth of the body weight of the

animal in kilograms, the concentration of the drug in the blood immediately upon complete mixing would be approximately 1000 mgm. per 100 cc. Within 30 minutes after the intravenous injection the concentration of the conjugated form of the drug has dropped to approximately 35 mgm. per 100 cc. This finding, together with the

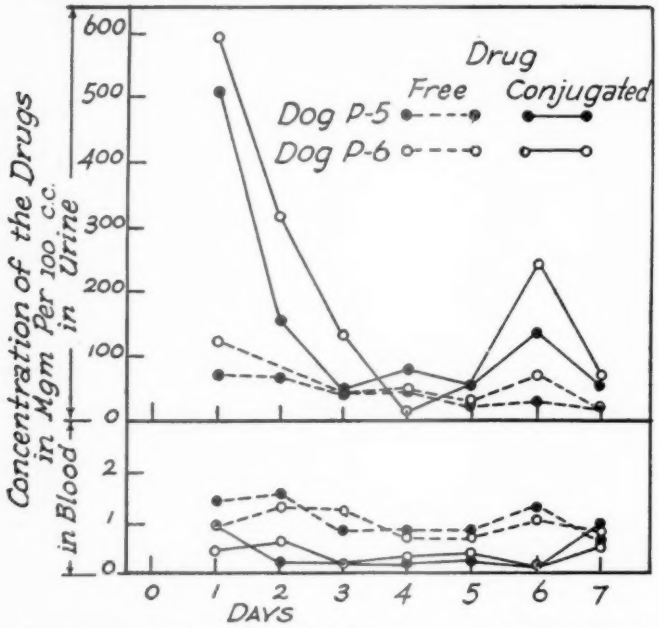


Chart 4. Rate of Excretion Following Repeated Intravenous Injection of the Sodium Salt Phthalylsulfathiazole. Dogs injected twice daily at twelve-hour intervals with 1.0 gram per kilo of body weight for a period of seven days; i. e., each animal received 14 grams per kilo of body weight of the phthalylsulfathiazole in the form of a 10 per cent aqueous solution of the sodium salt in seven days. The first specimens were taken twelve hours after the second dose. Thereafter daily specimens were taken twelve hours after the preceding injections.

very high concentration of the drug in the urine, indicates that phthalylsulfathiazole is very rapidly excreted by the kidneys. Dogs tolerate large intravenous doses of the sodium salt of phthalylsulfathiazole as indicated in Chart 4. It has been repeatedly observed that animals receiving phthalylsulfathiazole intravenously will have high urinary concentrations for the first 2-3 days of the injection. Thereafter, the urinary concentration will be considerably lower at a given time following the intravenous ad-

ministration. There is no evidence, however, that the drug is accumulating in the body because the concentration in the blood remains essentially the same.

Phthalylsulfathiazole has been administered intraperitoneally both as the free acid form in suspension in physiological normal saline solution and as a 10 per cent aque-

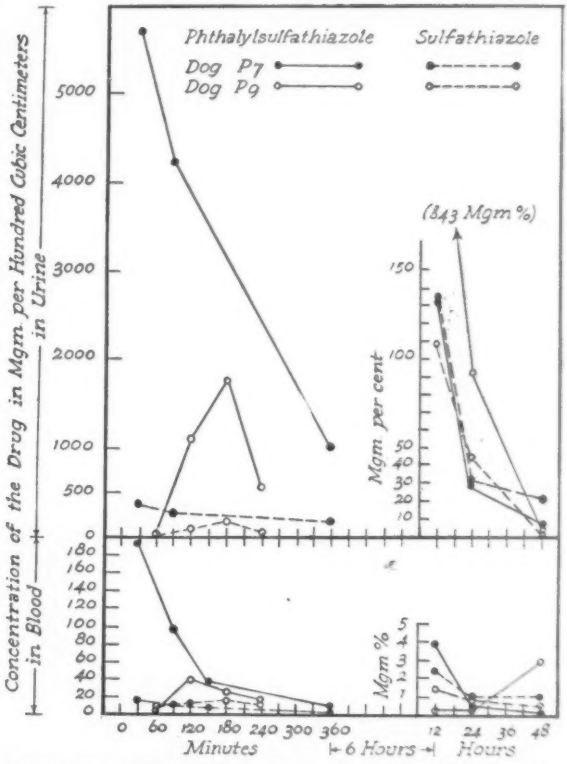


Chart 5. Intraperitoneal Injection: Dog P-7 received an injection of 1.0 gram per kilo of body weight of the sodium salt of phthalylsulfathiazole while Dog P-9 received an injection of 1.0 gram of the free acid form of phthalylsulfathiazole as a suspension in normal saline. It is observed that the concentration of the sodium salt in the urine is immediately high (6000 mgm.%) and decreases rapidly (135 mgm.%) within twelve hours. In the case of the free acid form, the urine concentration is lower, builds up more slowly, and then persists at a higher level (834 mgm.%) at twelve and twenty-four hour levels.

ous solution of the sodium salt. The concentrations of the drug in the urine and in the blood, as indicated in Chart 5, show that there is a considerable difference in the rate

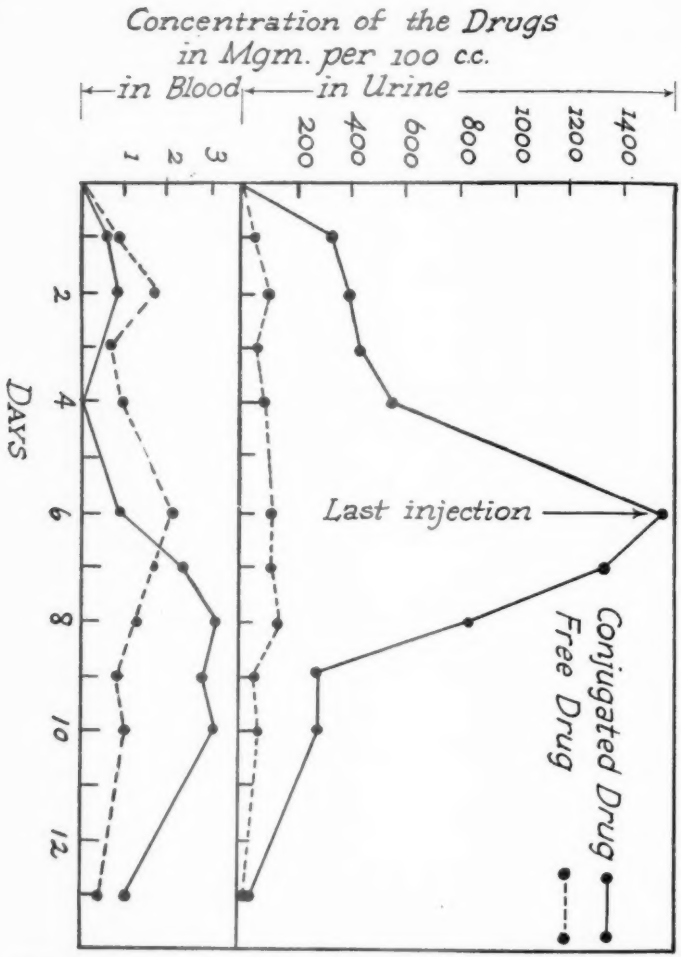


Chart 6. Absorption and Excretion of the Sodium Salt of Phthalylsulfathiazole Following Subcutaneous Injection. The charted data show the the concentrations of sulfathiazole and phthalylsulfathiazole in the blood and urine over a period of thirteen days during the first six days the dog received 1.0 gram per kilo of body weight of phthalylsulfathiazole in the form of a 10 per cent aqueous solution of the sodium salt. Specimens were taken daily just preceding injection on those days when additional drug was administered.

of absorption of the free acid form as compared to the aqueous solution of the sodium salt. This difference would, of course, be expected. It is obvious that the sodium salt,

while much more rapidly absorbed, is much more rapidly eliminated in the urine also. The free acid form of the drug maintains a higher concentration in the blood and in the excreted urine for a considerably longer period than its sodium salt, as indicated in Chart 5.

When the sodium salt of phthalylsulfathiazole is injected subcutaneously, it is rapidly excreted as indicated in Chart 6. However, if these injections are repeated

TABLE 3. The concentration of phthalylsulfathiazole in the blood following the oral administration of twenty-five (25) grams per kilo by gavage. The animal received a total of 160 grams, corresponding to one hundred times the therapeutic dose.

Hours after Administration	Concentration of the Drug in the Blood in Mgm. per 100 cc.	
	Free	Conjugated
1	2.6	0
4	3.1	1.7
24	1.8	0

daily, there is some cumulative effect in the tissues, as is reflected by the concentration of the drug in the urine. There is not, however, an increase in the concentration of the drug in the blood; this would indicate that there has been no demonstrable functional change in the urinary excretion.

Toxicity

Phthalylsulfathiazole and its sodium salts are so sparingly absorbed from the gastrointestinal tract that regardless of the dose, no toxicity can be demonstrated. Dogs have been maintained on an oral dose of phthalylsulfathiazole of 0.5 grams per kilo per day divided into six equal portions and administered at four-hour intervals for periods as long as six weeks without the development of evidence of toxicity. Autopsy studies on these animals failed to reveal either gross or microscopic evidence of toxicity, excepting for a slight amount of irritation to the mucosa of the bladder which occurred at the bladder neck. It should be stated that these animals were catheterized daily to obtain specimens of urine directly from the bladder, and that the irritation present might have been due to the manual trauma accompanying catheterization. Twenty-five grams per kilo of body weight of phthalylsulfathiazole

caused no symptoms when administered by gavage, Table 3. Three hours after administration the animal's stools were practically solid drug.

Following intravenous administration of 1.0 gram per kilo of body weight of the sodium salt of phthalylsulfathiazole in a 10 per cent aqueous solution, the animal usually vomited 5-6 times during the first 1-2 hours. Thereafter the animal recovers completely and will take food. Similarly, 1.0 gram per kilo of the drug was administered intravenously every 12 hours for a period of seven days. During this period each animal received 14 grams of phthalylsulfathiazole in the form of the sodium salt per kilo of body weight, and, since the administration was in 10 per cent solution, it was necessary to inject 10 cc. of fluid per kilo of body weight of the animal; the animal, therefore, was receiving the equivalent of a volume of solution approximately one-tenth that of his body volume every 12 hours. When the injections were first started, the animals would vomit after approximately one-fourth of the dose had been injected; however, after receiving several injections of the drug, the animals developed a tolerance, and the vomiting was much less severe and occurred once or twice only. During the period of injection, the animals salivated considerably. On the sixth day of administration, the feces of one animal were analyzed and showed to contain 2.6 mgm. of sulfathiazole and 7.4 mgm. of phthalylsulfathiazole per gram of stool. The coliform organisms were likewise significantly reduced to 60,000 per gram of wet stool. The animals did not eat well, lost some weight, and developed a mild degree of generalized muscular weakness. Before starting this intravenous administration, the right kidney and a biopsy specimen of the liver were removed. Animals were sacrificed 12 hours after the last intravenous injection. Complete autopsies were performed. No gross evidence of tissue damage was present except that there was occasionally a slight amount of peripheral congestion in the lungs, probably due to the large amounts of intravenous fluids which these animals had received at a rather rapid rate. Complete autopsy specimens were taken and microscopic examinations were performed by Dr. Paul Brindley, Professor of Pathology,

The University of Texas Medical Branch. His summary of a typical examination is: "Congestion and edema of the lungs, localized pneumonitis, cystitis mild; no very significant findings are seen in any of the tissues examined." In this connection it is interesting to note that one of the animals studied had an extensive pyelonephritis before the drug was administered. The following is a description of the microscopic examination of the kidney removed before the administration of the drug. "Microscopic examination of the kidney showed an extensive infiltration of both the medulla and cortex and pelvis by numerous lymphocytes and plasma cells along with a smaller number of polymorphonuclear leucocytes. The tubular epithelium shows granular changes and the presence of yellowish pigment granules. This kidney shows a rather extensive pyelonephritis." Following seven days' administration of phthalylsulfathiazole intravenously as outlined above, the animal was sacrificed and a complete postmortem examination carried out. Grossly the tissues appeared normal excepting for slight increased vascularity in the kidney capsule which was essentially similar to that noted on removal of the right kidney ten days previously. The following excerpt from the microscopic report by Dr. Bindley is quoted: "Sections of the kidney show a few collections of lymphocytes and plasma cells in the mucosa of the renal pelvis and similar cells are seen in scattered collections in both the cortex and medulla of this kidney. The lining cells of the convoluted tubules show granular cytoplasm and small granules of yellowish pigment. The blood vessels are not remarkable. At the tip of one papilla there is a small collection of bluish stain-material suggesting calcium." Comparison of the two kidneys showed quite conclusively that the pyelonephritis was less severe after treatment. One can assume, therefore, that no additional damage resulted because of the therapy, and it should be noted that these animals were excreting 2.0 grams of phthalylsulfathiazole per kilo of body weight daily, less the quantity excreted in the stools, after one kidney had been removed.

The subcutaneous administration of a 10 per cent aqueous solution of the sodium salt of phthalylsulfathia-

zole daily for a period of seven days gave no evidence of a toxic reaction either by clinical observation or at post-mortem examination. Tenderness develops at the injection site, but necrosis does not occur. In the case of intraperitoneal injection, however, there seems to be somewhat greater toxicity. On single intraperitoneal injection

TABLE 4. Comparison of the toxicity and bacteriostatic activity of some compounds having a varying structural, but chemical similarity to sulfanilamide, as indicated by the local effects on the coliform bacteria in the bowel of the dog.

Drug	Total Daily Dose Divided into 6 Daily Doses— Gms. per kilo	Comparative Antibacterial Action Against B. coli	Relative Toxicity
Sulfamino-benzoic acid	0.5 1.0	0 0	0
Sulfa-cyanamide	0.5 1.0	0	0 0
Sulfanilyl-isothio-urea	0.5 1.0	0	0 0
2 succinyl-amido-thiazole	1.0	0	
Succinyl-sulfanilic acid	1.0	0	
p-Succinyl-amino-benzamide	1.0	0	0

of a suspension of the acid form of the drug in 0.9% NaCl, an LD50 of 2.5 grams per kilogram is observed. Following the injection of a suspension of 1.0 gram per kilo daily for seven days without evidence of toxicity other than salivation, loss of appetite, vomiting during the first hours after injection, and some muscular weakness. A suspension of the free acid form of the drug in normal saline is not irritating. However, the injection of the sodium salt in ten per cent solution causes discomfort with spasm of the abdominal muscles.

An extensive toxicological study of phthalylsulfathiazole on laboratory animals other than dogs is being conducted by Mattis.

Chemically Related Compounds Not Sulfonamides

In Table 4 is given a group of compounds with certain structural characteristics similar to the sulfonamides. None of these substances, however, is a sulfonamide. These compounds have been studied in the same manner as the sulfonamides for local bacteriostatic activities in the gastrointestinal tract. None of these substances has, however, been investigated as a possible inhibitor of the sulfonamides. No antibacterial activity is shown by any of these compounds as would be indicated by the changes in the coliform flora in the bowel.

Mode of Action

The mechanism by which the sulfonamides act in the gastroenteric tract in the presence of the high population of bacteria and, no doubt, in the presence of varying quantities of substances which tend to inhibit the antibacterial action of the sulfonamides is not clearly understood. In a previous paper, the general mechanism of the possible local action of the sulfonamides in the gastroenteric tract was discussed. The competitive nature of the reaction between the sulfanilamide and its derivatives and the inhibitory substances such as p-aminobenzoic acid has been widely discussed by numerous authors (Fildes, 1940; Lockwood, 1941; Woods, 1940, and Wyss, 1941). In any consideration of the competitive action between the sulfonamides and the inhibitors, bacteriostasis will occur in the thermodynamic environment which will oppose the formation of the metabolic enzyme or the metabolite required by bacteria for multiplication.

Since the sulfonamides such as those studied in this series, having the p-amino group acylated, theoretically should have but slight bacteriostatic activity and which, in fact, have been shown to have little in vitro activity, it is only logical to assume that any antibacterial properties shown by these compounds should result from the deacylation of the conjugated compound. If this assumption were true, then one should observe the same changes in the bowel contents, regardless of which of these conjugated sulfonamides is used, and which would be dependent only upon the concentration of the free sulfonamide maintained in the bowel. The observed facts, however, do not

support such an hypothesis. For example, succinylsulfathiazole converts the feces to a relatively odorless, semi-fluid material in which the growth of coliform organisms is markedly suppressed. Phthalylsulfathiazole causes somewhat different changes. In this instance, the stools do not become as fluid, the odor is not reduced to the same degree, but the inhibition of the growth of coliform organisms is much more pronounced than is the case with the former drug. And again, in the case of phthalylsulfanilamide, the stools become semi-fluid and practically odorless, while there is only slight alteration in the coliform flora. These observations would support the claims that the characteristic odor of feces is not due to the coliform content, and would support the proposal that the odor is the result of the rather large group of loosely defined organisms called *Bacteroides* and anaerobic streptococci. Because of the complexity of the bacterial population of the bowel, it has not been possible to define with any degree of bacteriological accuracy which bacteria are inhibited by this series of compounds by their local antibacterial action in the bowel beyond showing that the coliform organisms and the clostridia are strongly inhibited.

These conjugated compounds intimately mixed with the bowel contents are present in large quantities and, because of their tendency to form salts through the free carboxyl group, these substances would be present in high concentration and even though they show but slight in vitro activity, the antibacterial action in these extremely high concentrations may very well be effective. It is not inconceivable that these compounds be absorbed or adsorbed by different strains of organisms to give a sufficiently high local concentration of the conjugated sulfonamide such that its own intrinsic action may be effective in inhibiting bacterial growth and also it might occur that certain strains of organisms would split the conjugated compound to give a high lethal concentration of an active nascent form of the deacylated derivative. It would not then be surprising to find a difference in the action of these different compounds dependent upon their various chemical and physical properties. It has been shown

previously that there seems to be a synergistic action between sulfathiazole and succinylsulfathiazole (Poth, Knotts, Lee and Inui, 1942). Throughout any such discussion as this, it must be remembered that the higher the concentration of the free sulfonamide found in the bowel, the greater is the

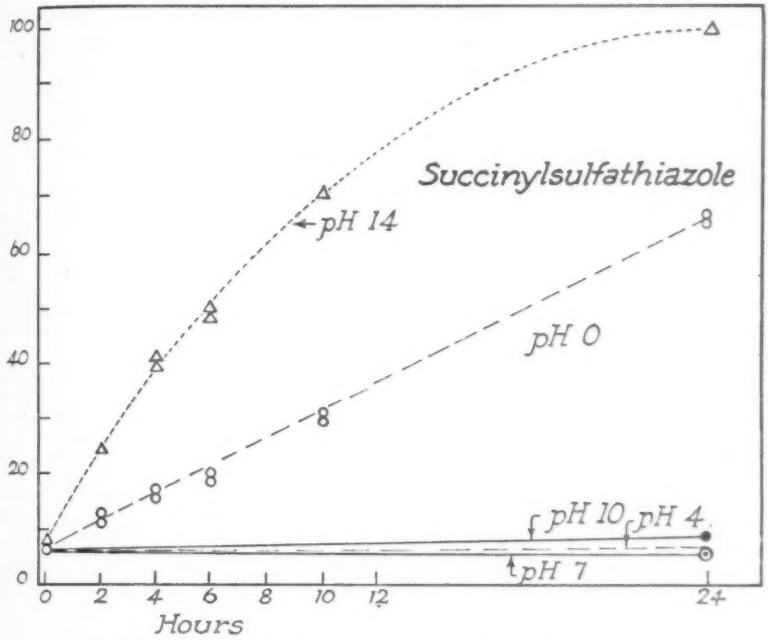


Chart 7. The graphic representation of hte rate o fhydrolysis of succinylsulfathiazole to yield succinic acid and sulfathiazole at different hydrogen ion concentrations. It is interesting that between pH 4 and pH 10 the rate of hydrolysis is extremely slow—being least at pH 7. The rate is moderately rapid in both 1 N HCl and 1 N NaOH solutions. each instance the succinylsulfathiazole concentration is 0.05 millimolar. Note: Duplicate determinations were made, but the points are not shown on the graphs for pH 4, pH 7, and pH 10, because of the lack of space.

alteration of the bacterial flora as indicated by the bacteriostatic effect upon the coliform organism.

A study of the hydrolysis rates of succinylsulfathiazole and phthalylsulfathiazole is most interesting and may help to explain some of the actions of these conjugated compounds. Attention is called to Charts 7 and 8, which show that, in the neighborhood of pH 7, the rates of hy-

drolysis of both succinylsulfathiazole and phthalylsulfathiazole are slowest. There is, however, a striking difference between these rates at different hydrogen ion concentrations. Succinylsulfathiazole is more rapidly hydrolyzed by one normal alkali than it is by one normal acid. In the case

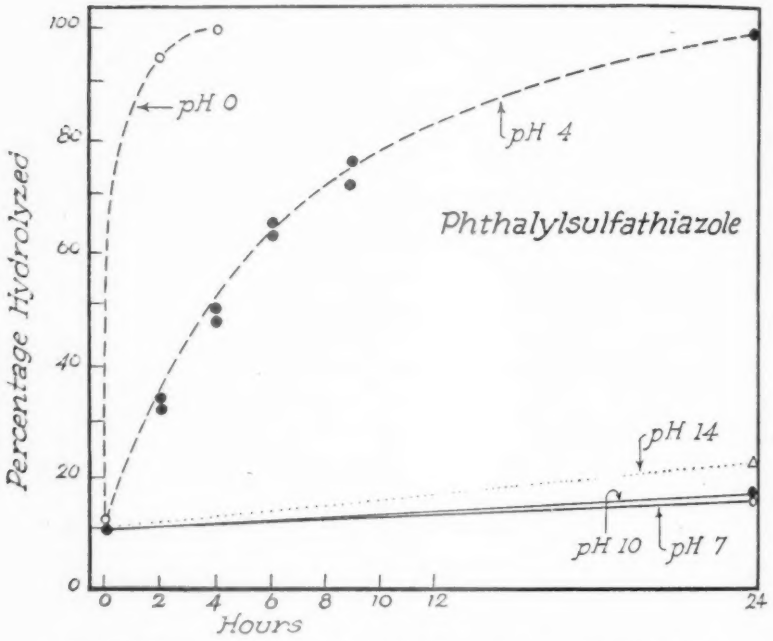


Chart 8. The graphic representation of the rate of hydrolysis of phthalylsulfathiazole to yield phthalyic acid and sulfathiazole at different hydrogen ion concentrations. It is interesting that phthalylsulfathiazole is quite stable in alkaline solutions, but that it undergoes rapid decomposition in acid solutions. At pH 0 the compound is extremely insoluable and is actually present as a finely crystalline suspension. In each instance, the phthalylsulfathiazole is present in such quantity as to yield 0.05 millimolar solution when completely soluable. The compound is in solution in all instances except at pH 0. Note: Duplicate determinations were always made, but the points are not shown because lack of space on the graphs.

of phthalylsulfathiazole, the rate of hydrolysis is very rapid in one normal acid, while in one normal alkali, the compound is relatively stable. This is even more pronounced when it is realized that in the presence of one normal acid, the phthalylsulfathiazole is highly insoluble and is present largely as a fine crystalline suspension. Therefore the curve which is drawn to represent the rate of hydrolysis

at pH O may in fact be a curve representing the rate of solution of the suspended crystals. The rate of solution may well be the rate determining reaction. It is not inconceivable that the difference in stability of these two compounds in acid and alkaline media may account for the observed difference in the consistency and odor of stools following the administration of these two drugs which in turn is due to the selective bacteriostatic activity of the two substances. Furthermore, if the mechanisms of action of this class of compounds include the absorption or adsorption of the conjugated derivatives by the individual bacterial cells, then these differences in rates of hydrolysis may again become operative.

Discussion

The continuation of the studies in the series of dibasic acyl derivatives of the sulfonamides has revealed another compound which promises to possess valuable therapeutic properties, through its antibacterial action locally in the bowel to alter the contained flora. This compound, phthalylsulfathiazole, is sparingly absorbed in the gastrointestinal tract and should, therefore, have little toxicity for the host.

Administered orally to dogs at four-hour intervals in doses four times the required therapeutic dose, the concentration of the drug does not exceed 3.3 mgm. per 100 cc. in the blood, and, given intravenously it is rapidly excreted in the urine. Following parenteral administration, the drug is excreted into the bowel to establish high concentrations of the compound and significantly alter the bacterial flora. The larger portion of this drug is excreted into the bowel by way of the bile.

As compared with succinylsulfathiazole, phthalylsulfathiazole has approximately four times greater antibacterial activity as is indicated by the reduction in coliform flora in the bowel of the dog. Gram for gram, phthalylsulfathiazole when ingested has shown no greater toxicity for the dog than has succinylsulfathiazole. On the basis of effective therapeutic doses, phthalylsulfathiazole would appear to have the lesser toxicity.

The mode of action of these acylated compounds is no doubt largely dependent upon their hydrolysis to give

the free active deacylated compounds. There is evidence, however, that this mechanism does not entirely explain the activity of these substances locally in the gastrointestinal tract. It is observed repeatedly that the various acyl derivatives of a single sulfonamide such as sulfathiazole do not bring about identical changes in the feces. If all of the antibacterial activity were due to the hydrolysis of the acylated derivatives to give sulfathiazole which would then be the sole agent causing the change in the physical characteristics and the bacterial flora, the changes in each instance should be identical. Such is not the case. While it is as yet not possible to give an accurate explanation of the differences observed, it is felt that a part of the local bacteriostatic activity of these compounds may be due either directly or indirectly to the intrinsic chemical and physical properties of these various conjugated derivatives of the sulfonamides.

Since phthalylsulfathiazole is less likely to form semiliquid stools than succinylsulfathiazole, it can be anticipated that the phthalyl derivative will be much more effective than the succinyl in the treatment of diarrheal diseases such as are encountered in the dysenteries, both bacillary and amoebic, and cholera in the human, and in the enteritides found among domestic animals, such as swine enteritis and white scours in new born calves. It can, likewise, be expected that this latter compound will be more effective in the presence of watery diarrhea because of its greater antibacterial activity.

Phthalylsulfathiazole has been successfully administered to man and the results of human administration will be the subject of a subsequent report.

Summary

In studying the local bacteriostatic activity of nineteen sulfonamides, including twelve new N^4-acyl derivatives, phthalylsulfathiazole was found to be a highly effective antibacterial agent which is sparingly absorbed from the gastroenteric tract, and which therefore exerts its activity primarily in the bowel and has low toxicity on oral administration.

The LD50 of phthalylsulfathiazole on intraperitoneal administration in the dog is 2.5 grams per kilo. Vomiting

follows intravenous injection of 1 gram per kilo of the sodium salt in 10 per cent aqueous solution. No evidence of toxicity appears in dogs on oral administration of 0.083 grams per kilo given every four hours for six weeks. At twice this dose the maximum concentration of the conjugated drug in the blood does not exceed 3.3 mgm. per 100 cc. With doses of 0.25 grams per kilo per day coliform organisms may be completely eliminated from the bowel after three days administration. Phthalylsulfathiazole has thus a bacteriostatic effect two to four times that of succinylsulfathiazole.

While rapid alkaline hydrolysis occurs in the case of succinylsulfathiazole, phthalylsulfathiazole undergoes quick acid hydrolysis, even though it is very insoluble in acid. These differences may be related to variations in the actions of these drugs, even though they might be expected to yield the same effective bacteriostatic compound on hydrolysis.

Phthalylsulfathiazole is less likely to form liquid stools than succinylsulfathiazole. The former may also be expected to be more effective in the presence of watery diarrhea than the latter, and it is predicted that "sulfathalidine" will prove to be highly effective in the treatment of acute enteric infections such as bacillary dysentery.

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While this article was in press, N. A. David and Associates at the University of Oregon School of Medicine published a report, with clinical observations on phthalylsulfathiazole generally agreeing with the conclusions reached here. *(West, J. Surg. Obs. Gyn., 51:419, 1943).* While selection of this compound from the series for detailed investigation was obviously based on our survey of the series, the Oregon studies were quite independent of those undertaken here.

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INVESTIGATIONS ON RICKETTSIAL DISEASES IN TEXAS

PART 3. SPOTTED FEVER: PROTECTION OF LABORATORY ANIMALS BY INTRADERMAL INOCULATION OF IMMUNE RABBIT SERUM

LUDWIK ANIGSTEIN, MADERO N. BADER, GERALD YOUNG AND DOROTHEA NEUBAUER*

The important role of the skin as a protective organ in the process of various infections is an obvious and well known fact. Nevertheless, the complex cutaneous apparatus which also serves as a portal of entry to numerous infective agents is being too often neglected in our procedures of protective vaccination. In fact, in all our routine vaccinations with suspensions of killed bacteria the epidermis is penetrated and thus deliberately avoided. This includes the immunization against agents to which our skin is particularly susceptible and against which the immunization of this tissue would be the first and logical step.

Veterinary medicine has taken, however, advantage of the above facts in using intradermal vaccination against some infections where the skin is the portal of entry and to which it is also especially susceptible.

A classical example in this respect is anthrax against which the intradermal vaccination with living attenuated cultures of *B. anthracis* has been used with success. It is of interest to recall that a single intradermal injection of a minute dose of this vaccine confers to sheep an instant, almost "explosive" general immunity (Besredka, 1928, p. 257) and is much more effective than the subcutaneous method.

The intradermal route of vaccination has also proven successful in some virus diseases, particularly in equine encephalomyelitis. In their recent work Schoening, Shahan, Osteen and Giltner (1940) made a comparative study of the value of the intradermal and subcutaneous routes of vaccination of guinea pigs and horses against encephalomyelitis. In a series of preliminary tests on guinea pigs

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Paper read before the Spring meeting of the Texas Branch of the Society of American Bacteriologists, Dallas, Texas, May 8, 1943.

the above authors showed that these animals could not be protected by a single subcutaneous injection of 0.05 cc. of the virus, as none of the animals survived the subsequent reinfection. When, however, the same amount of virus was injected *intradermally* the rate of survivals was equal to 16.7 per cent. In experiments on horses the intradermal vaccine gave at least as good results when administered in two doses of 1 cc. as did the two 10 cc. doses given subcutaneously. In some experiments even a single injection of 0.5 cc. of the virus conferred to the horse solid immunity against encephalomyelitis.

The above observations clearly demonstrate the superiority of the intradermal vaccination against certain infections. Evidently, there is an inherent quality of the skin possibly due to its dense texture and to a certain physiological autonomy by which the skin is acting not only as a mechanical barrier but also as an immunological entity. It is most probable that the slow diffusion of the stimulating antigen and its longer persistence in the skin may lead to a greater production of antibodies than by any other route of inoculation.

On the basis of the above facts and considerations *the intradermal route for separate inoculation of spotted fever virus and immune serum was chosen in the present work with the attempt of protecting a susceptible animal against the virus and of creating a solid immunity.*

The principle of separate inoculation of virus and immune serum is not new; it has been practiced in veterinary medicine as well as in the prevention of some human infections. Swine are successfully vaccinated against hog cholera by the virus and immune serum injected at the same time but in different sites and so are cattle against rinderpest. As a whole, this method has proven successful although on rare occasions the subcutaneously inoculated immune serum failed to protect the animal against the deadly virus. As will be seen later our method although different by its intradermal application can be in principle compared with the early immunization of man against yellow fever (Sawyer, Kitchen and Lloyd, 1932). An active immunity also developed in monkeys which were protected against yellow fever virus by a simultaneous or previous

injection of immune serum. The effect of separate inoculation of virus and immune serum was studied in recent years on the vaccinia virus in which it was shown that infiltration of the susceptible skin with immune serum affords protection against subsequent inoculation with the homologous virus. It has thus been shown by Andrewes (1928), Fairbrother (1932) and recently by Green and Parker (1942) that it is possible to protect an animal against vaccinial infection when the infiltration of the skin with immune serum follows the vaccinia virus within a suitable time.

Attempts were made previously by one of us (L. A.) to protect guinea pigs against the virus of louse-borne typhus by infiltrating a limited skin area with homologous convalescent serum. After an interval of several hours, the virus was then injected intradermally into the infiltrated area. Out of 42 guinea pigs thus treated only three developed typhus while 39 did not react to the virus and subsequently proved immune to reinfection with typhus (Anigstein, 1936).

On the basis of the above results it was of interest to know whether similar results could be obtained with spotted fever.

The results of serum prophylaxis in rickettsial diseases so far are not uniform and generally are not satisfactory. The same was true for serum therapy until recently when an effective immune rabbit-serum of high potency was elaborated by Topping (1940) for Rocky Mountain spotted fever. The amount of serum used by Topping in guinea pigs was originally 5 cc. given subcutaneously daily on the first two days of fever. Although the serum had no immediate effect on the high fever level, the disease of the treated animals was of shorter duration when compared with the controls. In contrast to the untreated animals of which all died, the treated guinea pigs remained alive.

More recently it was found by Topping (1943) that a single injection of 0.5, 0.25 or 0.1 cc. of twentyfold concentrated rabbit-serum administered on the first day of fever was effective in preventing death. If the serum was administered 24 hours after the infecting dose, there was a complete suppression of recognizable spotted fever. If

48 hours elapsed, the disease was modified. The same applies when the serum was given 72 hours after the infective injection, but if the serum was given on the second day of fever there was practically no effect.

As will be seen later the problem was attacked by us from a somewhat different angle, as we are primarily interested in the prevention of spotted fever, while Topping's work is directed toward serum therapy.

A specific serum was produced by the writers by repeated inoculations of rabbits with Rocky Mountain spotted fever tick-vaccine which was previously shown to protect fully also against spotted fever of Texas origin (Anigstein and Bader, 1943, p. 136). The virus used in this study was one of the strains isolated in Texas by the above authors.

The rabbit immune serum was produced by inoculating rabbits intravenously with the Dermacentor tick-vaccine and Cox eggyolksac-vaccine, 2 cc. each time, at seven-day intervals. A total of four injections was given to each rabbit, followed by a final subcutaneous injection of living virus in form of spleen emulsion from an infected guinea pig. Rabbits were bled to death a fortnight after the last injection and the serum was then preserved in Merthiolate (1:10,000) and kept in the refrigerator. This method by which less antigen was used as compared with Topping's technic also differs from that of Topping (1940) who after several vaccinations of rabbits with the tick-vaccine used live infected ticks as inoculum. Furthermore, contrary to the twentyfold concentrated serum used by Topping and manufactured by Lederle Laboratories, New York, our product is unrefined rabbit immune serum. It can be, therefore, assumed that the actual antibody content of our rabbit serum is equivalent to one-twentieth of that used by Topping.

In a series of experiments described below three factors were considered: First, the *site of inoculation* of virus and serum, secondly, the *time* factor, and finally the *amount* of immune-serum.

A rectangular area (half square inch) of the shaved abdominal skin of guinea pigs was delineated with indelible pencil and minute amounts of the immune rabbit serum were injected intradermally at each of the angles directing the 27 gauge needle toward the center of the square. Apart from the wheals produced by the injection,

the whole delineated area gradually developed a slight swelling largely due to the infiltration with serum.

The above procedure was adopted in a series of experiments in which 0.1 cc. of the serum injected at each of the four angles was followed by intradermal inoculation of 0.1 cc. of virus (spleen suspension of infected guinea pig) in the center of the square, two hours later.

The results in spotted fever correspond to those mentioned above in louse-borne typhus, namely, the guinea pigs did not develop fever and proved immune to subsequent reinfection with the virus.

In the great majority of cases, the serum was inoculated at the same site into the shaved abdominal skin of guinea pigs either simultaneously or subsequently to the virus. Out of a series of fifteen guinea pigs in which 0.1 cc. virus and 0.4 cc. immune serum were inoculated almost simultaneously, eleven failed to react with any elevation of temperature while four developed spotted fever. Three of the non-reacting animals proved completely immune to a subsequent reinfection with spotted fever (Table 1). A control experiment included six guinea pigs treated with the same amount of serum given at the same time with the virus, but at *different sites of the body*. Of these six guinea pigs, five developed typical spotted fever, while only one failed to react.

It is clear from the above results that the specific antibodies contained in 0.4 cc. of immune serum protected the majority of guinea pigs against spotted fever when both virus and serum were inserted at the same site. It is, therefore, logical to assume that a neutralization of the virus by the serum took place before the virus became fixed by the tissue. A complete inactivation of the virus was thus attained in eleven guinea pigs, four of which, however, did not prove to be immune to a subsequent reinoculation.

The efficacy of the immune rabbit serum has been compared with that of convalescent guinea pigs sera. For this purpose a series of ten guinea pigs all of which were recovered from typical spotted fever infection of Texas

origin were bled to death within a period of time from 3-6 weeks of convalescence. Their serum was then pooled and used in the same way as the rabbit immune serum, i. e., 0.4 cc. intradermally and simultaneously with 0.1 cc. of virus. Of four guinea pigs treated with pooled convalescent guinea pig sera all developed typical spotted fever just as the control animals. Similar results were obtained when normal rabbit serum was used for control tests (Table 2).

In the next series of tests smaller amounts of immune serum were used: Three guinea pigs were treated with 0.1 cc. of immune serum, four with 0.05 cc. and six with 0.025 cc. all injections being given simultaneously with the virus and intradermally at the same site. Out of the total of thirteen guinea pigs of this series none developed fever during the two weeks observation (Tables 3 and 4).

Two weeks later they were all reinoculated subcutaneously with 0.5 cc. spleen emulsion (one spleen in 5 cc. of saline) from a spotted fever guinea pig. All the control animals developed typical spotted fever. Nine of the test guinea pigs showed complete immunity while three showed partial medium grade immunity. The last group treated with 0.025 cc. of serum developed fever after seven days' incubation, the fever lasting only three days. Judging from these experiments the best results were obtained with 0.1 and 0.05 cc. of our serum while 0.025 cc. was found under the above circumstances to be on the borderline of efficacy (Tables 3 and 4).

It was obviously of practical interest to investigate whether the small quantities of immune serum would protect animals *subsequent* to virus inoculation.

For this purpose twenty guinea pigs, inoculated intradermally with 0.1 cc. of spleen emulsion of a spotted fever guinea pig, were divided in five groups of four animals each. Each group was then injected intradermally with 0.025 cc. of immune serum at the site of virus administration at different intervals of time: for example, after a lapse of one hour, two, three, four, six and eighteen hours. None of the twenty treated guinea pigs developed any febrile reaction while all the control animals showed typical spotted fever. Three of the test animals died from an intercurrent infection, leaving seventeen for immunity tests.

The latter were reinoculated with virus (0.5 cc. subcutaneously) one month after the first virus inoculation and all remained afebrile during the next two weeks of observation (Tables 5 and 6).

We then extended the serum protection tests over twenty-four and forty-eight hours. In the first series of five guinea pigs treated with 0.4 cc. of unrefined immune rabbit serum twenty-four hours after intradermal virus inoculation all remained afebrile during fifteen days' observation. Two weeks later they were reinfected subcutaneously with guinea pig spotted fever virus (0.5 cc. of heavy spleen suspension) and all proved immune (Table 7). Of seven control guinea pigs, six reacted with typical high fever.

Identical results were obtained when the above serum dosage was administered forty-eight hours later at the same site of virus inoculation. Of four guinea pigs which all remained afebrile one died after twelve days of observation. The remaining three were subsequently reinoculated with the passage virus and were all released immune, while seven control animals reacted typically (Table 8). When, however, the serum was given on the day preceding the onset of fever, no effect was noticed whatsoever (Table 9). This period of time usually coincided with a sharp drop of body temperature of the guinea pig to subnormal level and was rapidly followed by an abrupt, explosive rise of fever as recorded the following morning. The critical drop of temperature at the very end of incubation which was observed regularly in the intradermally infected control animals was striking and is worth noting. It was highly pronounced in guinea pigs inoculated by intradermal route in contrast to those infected intraperitoneally. This observation may throw some light on the mechanism of this infection which apparently consists of two phases: one expressed by the limited proliferation of rickettsiae in the cutaneous tissues where the phenomena of the interplay of the virus and specific antibodies apparently take place. The next phase is marked by the virus breaking through the defenses of the skin barrier and resulting in a generalized unrestricted invasion. This phase

which is preceded by a critical drop of body temperature is accompanied by a sheer rise of high fever. If at this moment, when the invasion begins immune serum is administered no protective effect can be expected (Table 9).

It seems, therefore, that the mechanism of infection particularly the active role of the skin is a conspicuous factor which influences the issue of the immunological reactions (protection and immunity).

It was, of course, of interest to determine whether the above method would make it possible to prevent the disease when the original tick-virus is used.

The source of tick-virus were male ticks *(Dermacentor andersoni)* infected with Rocky Mountain spotted fever and supplied by courtesy of Dr. R. R. Parker, Director, Rocky Mountain Laboratory, Hamilton, Montana. Five of these ticks were ground in 5 cc. saline and 0.1 cc. of the emulsion was injected intradermally into each of nine guinea pigs. The skin of each of the six animals of this series was then infiltrated with 0.4 cc. of immune serum at the site of virus inoculation after an interval of four hours while the remaining three guinea pigs were left as controls. The latter group promptly developed typical spotted fever after an incubation of four to six days, while all the treated animals proved fully protected against the virus.

Discussion:

In analyzing these phenomena we have to admit that the minute doses of 0.1, 0.05 and 0.025 cc. of unrefined immune rabbit serum could hardly afford any degree of passive immunity. We may presume, however, that the virus absorbed by the immune serum in the tissue acted as a sensitized vaccine. It is also possible that the above amounts of serum were unable to check the virus completely, leaving an avenue of escape for a fraction of the altered virus. A symptomless infection would then result affording a solid immunity to guinea pigs. This interpretation would explain the apparent puzzling phenomenon why some guinea pigs treated with the same dose of virus (0.1 cc.) but with larger amounts of immune serum (0.4 cc.) did not develop immunity. Under these circumstances the virus was evidently rendered completely innocuous and its antigenic properties destroyed by the excess serum.

Whatever the intrinsic nature of the phenomena may be, they strengthen the emphasis laid originally by Besredka (1928) on the role of the skin in infection and immunity. Due to a certain biological autonomy of the skin as an organ it is possible to create a local immunity by introduction of a pathogenic agent (bacterial or viral) which phase is eventually followed by a general and solid immunity. In the present studies an interception of the virus has been attained in various degrees at the site of the original injection by employing varying minute amounts of specific serum. The longest interval of time after which this interception was still possible under the above circumstances was forty-eight hours.

★

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TABLE 1.

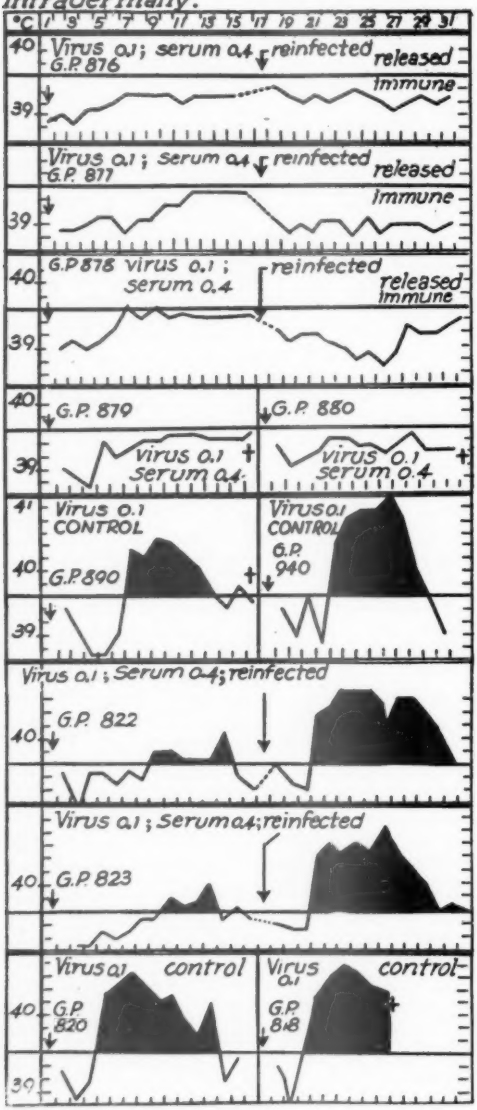

Virus + serum simultaneously, same site.
intradermally.
°C
1 3 5 7 9 11 13 15 17 19 21 23 25 27 29 31
40
39
Virus 0.1; serum 0.4
G.P. 876
reinfected
released
immune
Virus 0.1; Serum 0.4
G.P. 877
reinfected
released
Immune
G.P 878 virus 0.1;
serum 0.4
reinfected
released
immune
G.P. 879
G.P. 880
virus 0.1
serum 0.4
41
Virus 0.1
CONTROL
G.P. 890
Virus 0.1
CONTROL
G.P.
940
Virus 0.1; Serum 0.4; reinfected
G.P. 822
Virus 0.1; Serum 0.4; reinfected
G.P. 823
Virus 0.1
control
G.P.
820
Virus
0.1
control
G.P.
818

TABLE 2.

Control tests with normal rabbit sera + convalescent guinea pig sera

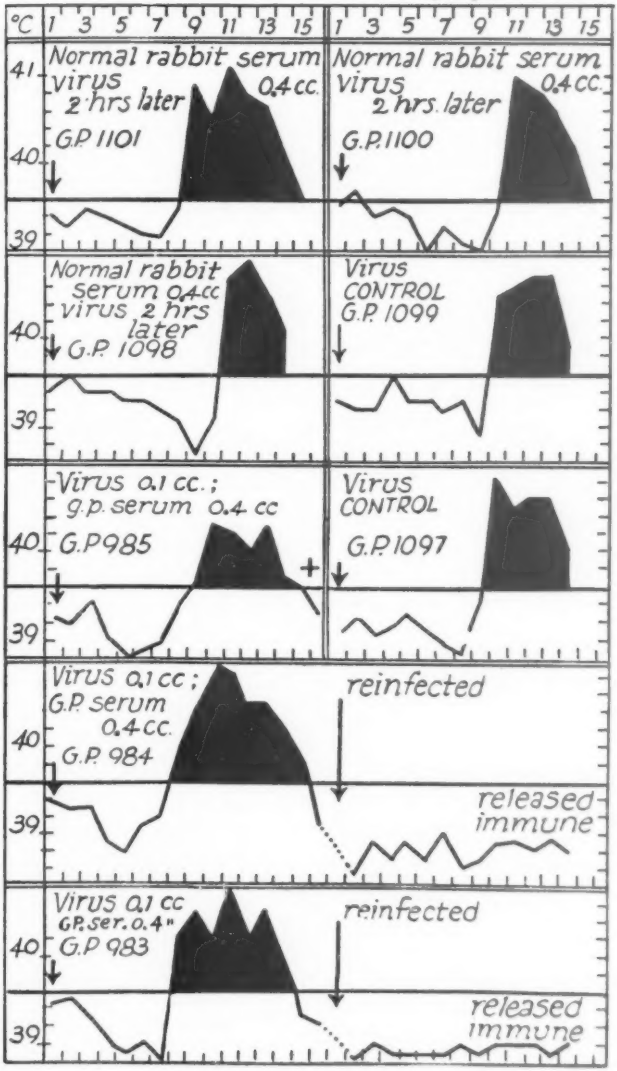


TABLE 3.

Virus + serum simultaneously; same site; intradermally.

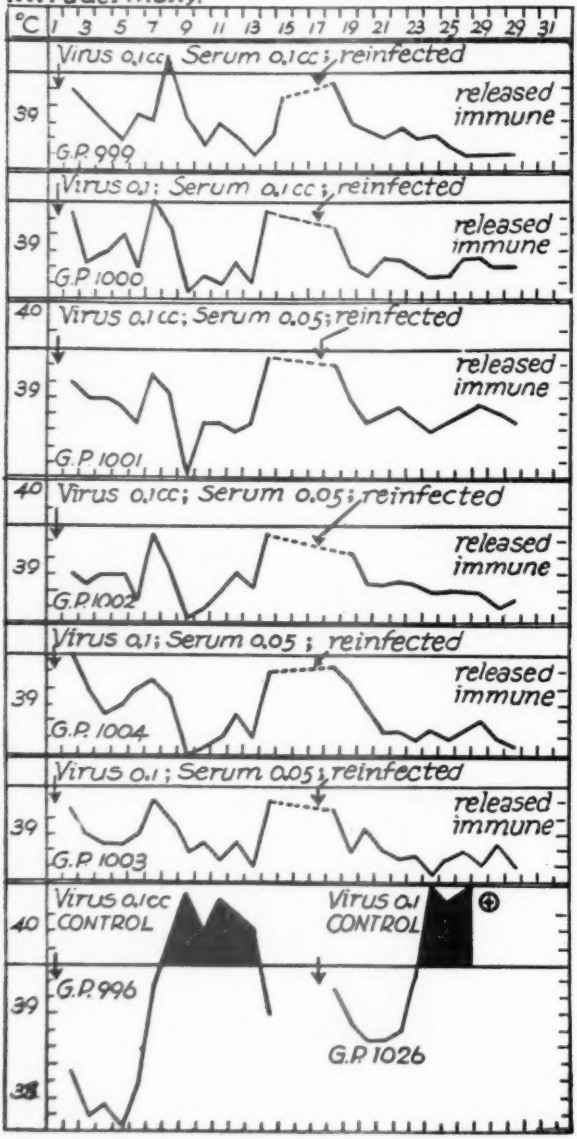


TABLE 4

Virus + serum simultaneously; same site; intradermally

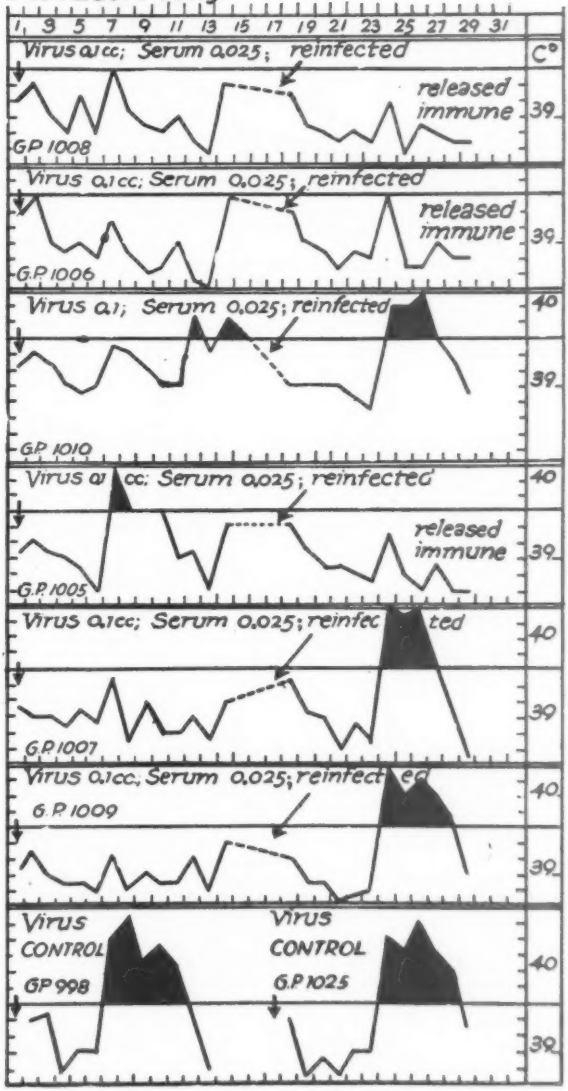


TABLE 5.

0.025 c.c. immune serum subsequent to virus; same site: intradermally.

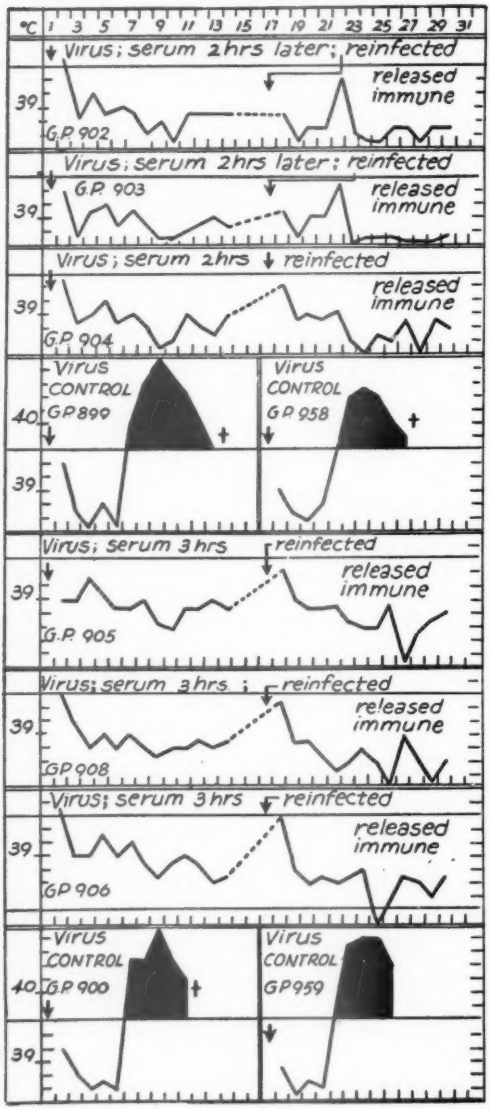


TABLE 6

0.025 c.c. immune serum subsequent to virus: same site: intradermally.

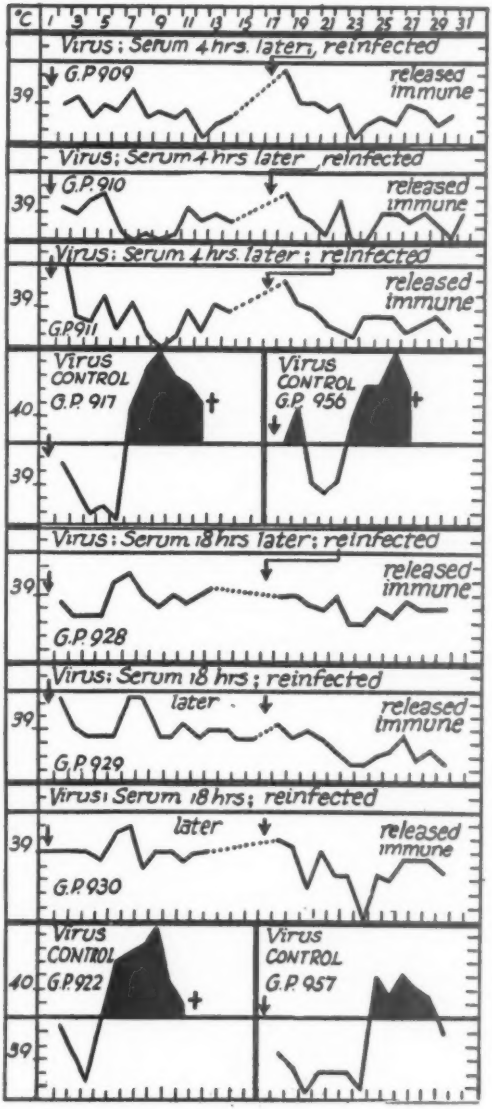


TABLE 7.

Immune serum subsequent to virus; same site; intradermally.

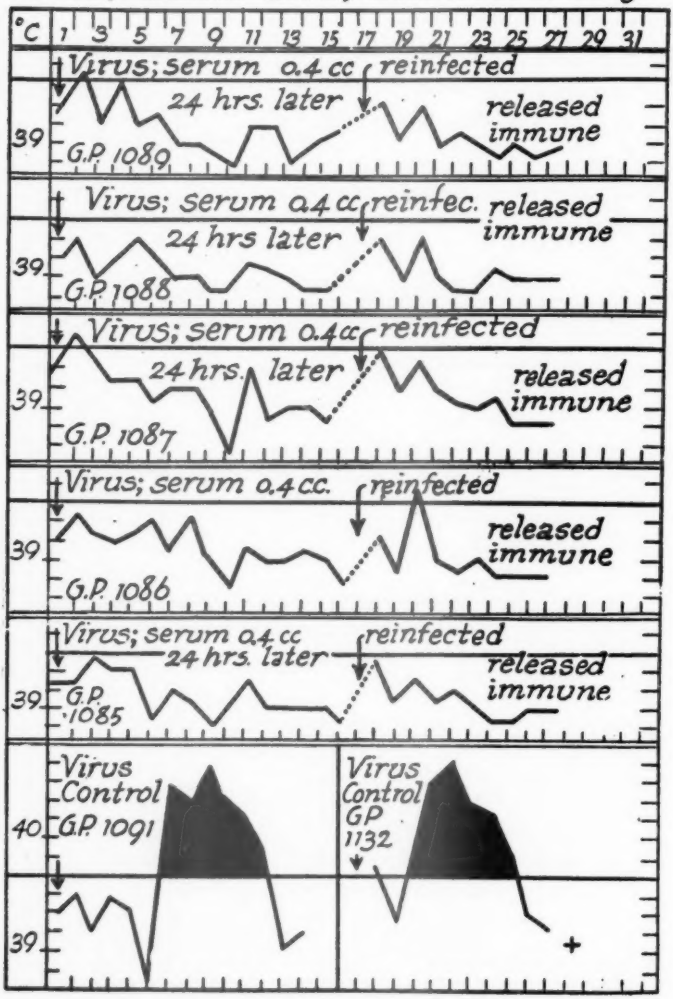


TABLE 8

Immune serum subsequent to virus; same site; intradermally.

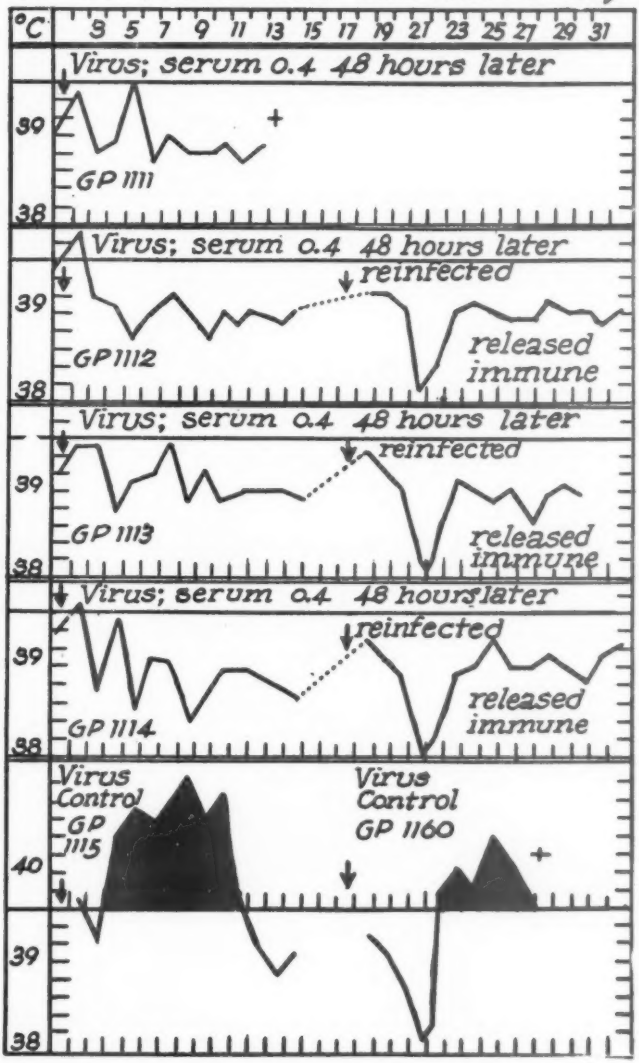
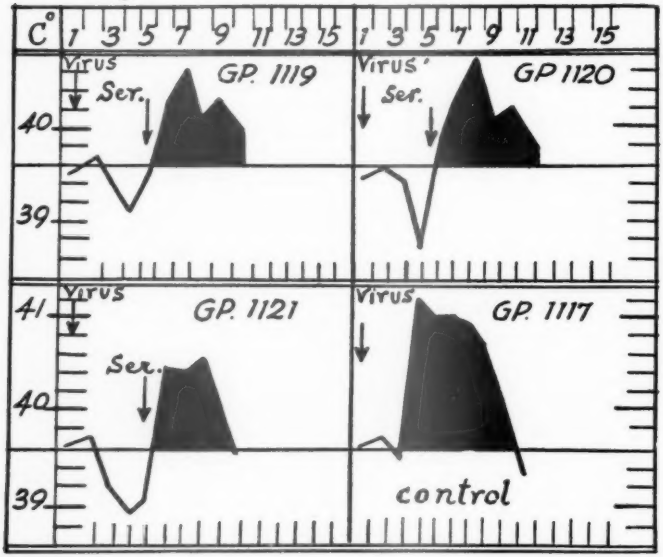


TABLE 9.

Failure of immune serum to protect when given at end of incubation.



INVESTIGATIONS ON RICKETTSIAL DISEASES IN TEXAS

PART 4. EXPERIMENTAL STUDY OF BULLIS FEVER.

LUDWIK ANIGSTEIN AND MADERO N. BADER*

A clinical syndrome of an apparently new disease was observed during the summer seasons of 1942-43 among army troops at Camp Bullis—a military reservation area, sixteen miles west of San Antonio, Texas†.

According to the recently published account (1943) of Colonel J. C. Woodland, Major M. McDowell, and Captain J. T. Richards, all of the Medical Corps, U. S. Army, 485 cases of Bullis fever have been admitted to the Brooke General Hospital, Fort Sam Houston, Texas, during May and June, 1943. Approximately the same number was observed the preceding summer making a total of about one thousand cases. The condition can be characterized as an acute febrile disease with abrupt fever lasting from 4-14 days and accompanied by severe headache. Generalized lymphadenopathy and a marked leukopenia were the constant findings. In more severe cases a maculopapular rash was noted. The Weil-Felix reaction was recorded as negative. The complement fixation yielded negative results for Q fever, Rocky Mountain spotted fever, and typhus fevers.

Since the disease could not be identifed with any known condition, the above authors consider it as a new disease entity.

Although the clinical course can be rather severe and the disease debilitating, the fatality rate is practically nil. There are indications, however, that the disease is increasing in severity.

It is obvious from the foregoing that the mass outbreak of the disease within a limited period of time had a distinct epidemic character. The presence of a common epidemiological factor was, therefore, a logical assumption. In this respect the heavy tick infestation of the Camp

*From the Department of Preventive Medicine and Public Health, University of Texas, Medical Branch. With technical assistance of Miss Dorothea Neubauer. Received for publication September 28, 1943. Paper read before the Fall meeting of the Texas Branch of Society of American Bacteriologists, Austin, Texas, November 13, 1943.

†Camp Bullis was named for Brig. Gen. John L. Bullis, U. S. Army, a famous Indian fighter and scout.

Bullis area by *Amblyomma americanum* and the tick-bite history of all the cases pointed from the beginning to this tick as the probable transmitting agent (Woodland, McDowell, and Richards, 1943). Besides, the possible role of the mite *Trombidium irritans* (red bug, chigger) which also readily attacks man has been mentioned by Livesay and Pollard (1943). The presence of this mite, other species of which *(T. akamushi* and *T. deliensis)* are vectors of tsutsugamushi in the Far East (Japan and Malaya) cannot be entirely ignored. In fact, tsutsugamushi would be the only human rickettsiosis which to some extent resembles clinical Bullis fever, namely, by generalized lymphadenopathy and leukopenia (Anigstein, 1933; Lewthwaite and Savoor, 1940).

One of us (L. A.) who early in July, 1943, participated in the military training course at Camp Bullis had the opportunity of acquainting himself with the scene of the outbreak as well as with the frequency of tick bites.

The military reservation of Camp Bullis covers a vast area of some 30,000 acres of rolling, mostly rocky country at an altitude from 1000 to 1400 feet. The flora is dominated by live oak, juniper, tall grass and various kinds of shrub. The mammalian fauna according to the information supplied by Dr. James M. Brennan, zoologist, assigned to the Post Surgeon's Office, can be enumerated in the order of decreasing prevalence as follows:

Deer, jack rabbit, armadillo, cotton-tail rabbit, fox, fox squirrel, racoon and some 24 species of birds.

A systematic tick survey was previously carried out on a large scale by Dr. Brennan who collected the ticks from the above mentioned animals as well as from the ground by dragging. The predominant tick was *Amblyomma americanum* (about 98 per cent), the remainder being *Haemaphysalis leporis-palustris* (the rabbit tick), and other species. In view of the overwhelming preponderance of the "Lone Star" tick which has been recently found a carrier of spotted fever (Anigstein and Bader, 1942, 1943; Parker, Kohls and Steinhaus, 1943) and also found infected in nature with Q fever rickettsiae in Texas (Parker and Kohls, 1943) our attention was primarily concentrated on this tick as a possible carrier of Bullis fever.

Simultaneously and independently a study of this subject has been inaugurated by the War Department with the appointment of a "Commission for the study of Bullis fever." While the investigations of this commission, as well as our own work, began in the first half of July, 1943, the Eighth Service Command Laboratory, Fort Sam Houston, Texas, was engaged in experimental work on Bullis fever since 1942 using almost entirely human material from Bullis fever patients (Livesay and Pollard, 1943). Significant results were achieved by these authors who have noted in smears of peritoneal scrapings from guinea pigs injected with blood of Bullis fever patients "small rods and coccoid bodies in the cytoplasm and in the nucleus, rickettsia-like in morphology." Small intracellular fuchsinophilic granules and rods (Macchiavello staining method) similar in morphology to rickettsiae were also observed by the above authors in lymphnodes from Bullis fever patients. The response of guinea pigs to the inoculation with blood of Bullis fever patients was a consistent low grade febrile reaction which usually lasted one or two days after 9-11 days of incubation (Livesay and Pollard, 1943). Swiss mice injected with infectious tissue showed no evidence of disease but when killed on the ninth day exhibited splenomegaly. Masses of intracellular rickettsia-like organisms, more numerous than in guinea pigs were found by the above authors in the organs of these mice.

CHARACTERISTICS OF THE DISEASE IN GUINEA PIGS

A. *Symptomatology.*

Our own studies began on July 12, 1943, when 500 adult ticks from Camp Bullis kindly supplied by Dr. J. M. Brennan and identified by him as *Amblyomma americanum* served as the starting point of the investigations. The ticks were divided in five batches of 100 each and after a thorough rinsing in saline each group was triturated and injected intraperitoneally into six guinea pigs, thus involving thirty guinea pigs for the first series of experiments.

Generally speaking, the febrile reactions of guinea pigs to the direct inoculations with the ticks showed fevers of the most erratic character: elevations of one day dura-

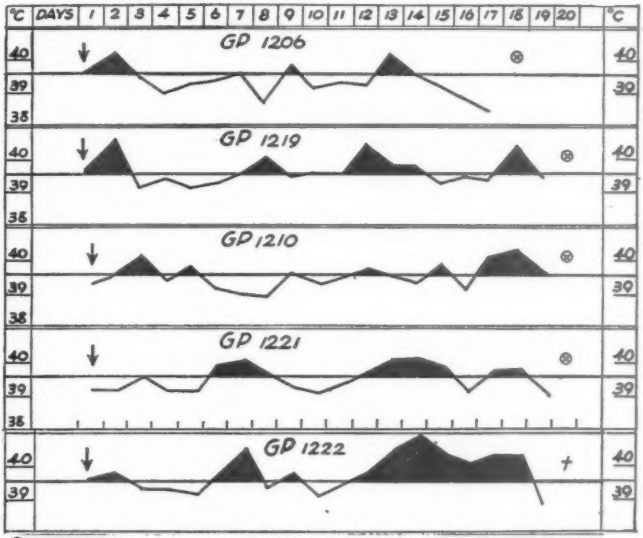
tion after twelve days incubation, repeated attacks of one to two days duration in almost regular, three to four days intervals, then continuous high fevers after five days incubation and, finally, irregular and protracted low-grade fevers. (Table 1.) The first group of inoculated guinea pigs showed a fairly uniform response, namely, in three guinea pigs a synchronized rise of temperature was noted after twelve days incubation, the fever lasting one day only, in other two guinea pigs the first short febrile reaction appeared on the fifth day of incubation but was followed by one and two days fever on the twelfth day. One guinea pig of this series did not react.

In the second group, fevers of two days duration appeared after an incubation period of eleven to twelve days, while one animal of the same series produced high and continuous fever five days after inoculation of ticks; two animals of this group remained afebrile. Rather irregular fevers were observed in the next two groups while in the last group of five a sharp rise of temperature occurred synchronically in three guinea pigs. Two of them were killed for passage on the third day of the subsiding fever.

In dealing with a new infectious agent it was, of course, difficult to decide offhand whether this variable symptomatology was due to one or several factors. Despite the various fevers observed the immunological tests of our convalescent guinea pigs to Bullis fever of human origin indicate as will be seen later a uniform nature of the infection from ticks. The strain isolated originally from one hundred pooled specimens of *Amblyomma americanum* is maintained in guinea pigs by passages in using the spleen, liver, or blood as inoculum and has reached thus far its twelfth generation. (Table 4.) A great variety of febrile reactions was encountered during these passages, contrary to other experimental rickettsioses to which guinea pigs usually react with a definite type of fever following a certain period of incubation, characteristic for each of the diseases. In Bullis fever a passage originating from a guinea pig killed at the fifth day of high continuous fever may result in two days fever reaction, while in another case fever of one day duration will provoke in the next passage a fever lasting eight days or so. In addition, relapsing types of short fevers were observed in the course of the transfers, in other

words, various febrile reactions were reproduced similar to those occurring from direct inoculations with ticks. Positive results were obtained when transfers were made irrespective of the stage of infection, also during the relapses of short duration. Some infected guinea pigs remained afebrile dur-

I. Fever charts of guinea pigs inoculated directly with ticks (Amblyomma americanum) from Camp Bullis, Tex.



⊗ Released immune to Bullis fever strain of human origin
† Not immune to spotted fever

ing the three weeks' observation period. Blind passages were then made from these inapparent infections with the result that fever reactions reappeared in the next transfer or in the one following it. (See Table 4, gpgs. 1358 and 1373.) Thus far, no information was obtained as to the persistence of the infectious agent in guinea pigs during their convalescense.

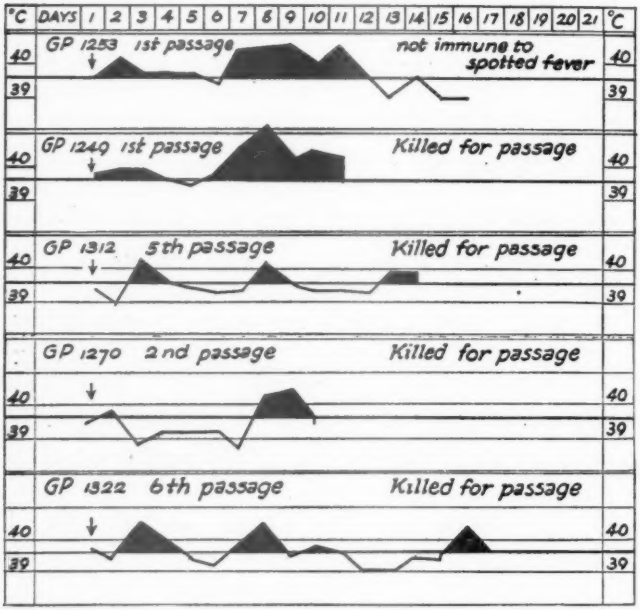
The similarity between our fever charts and those of experimental Bullis fever of human origin is significant. (Tables 1, 2, 3.)

*The first four of the above group were subsequently tested against human Bullis Bullis fever strain and found completely immune.

B. Pathological lesions.

In general, the gross pathology was conspicuous only in the series of guinea pigs directly inoculated with ticks or in the early passages while in later transfers the changes were of slight intensity. These lesions involved inguinal

2. Fever charts of guinea pigs in various passages of the strain isolated from ticks (Amblyomma americanum) from Camp Bullis, Texas

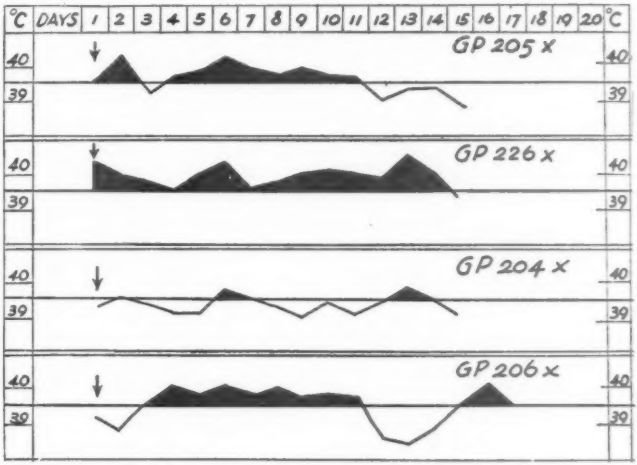

°C
DAYS 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21
°C
GP 1253 1st passage
not immune to spotted fever
GP 1249 1st passage
Killed for passage
GP 1312 5th passage
Killed for passage
GP 1270 2nd passage
Killed for passage
GP 1322 6th passage
Killed for passage
40
39

and axillary lymphnodes which were found swollen and usually injected. This condition was first observed in guinea pigs inoculated with ticks and killed at the third day of fever and in the next transfer guinea pigs. In later passages, however, slight or no changes in the lymphnodes were found.

The next organ affected is the spleen which in the majority of febrile guinea pigs was enlarged, dark and friable, its surface smooth showing sometimes an opalescent film. In few instances a greyish fibrinous pseudo-membrane

was found resembling that in tsutsugamushi and Q fever. As compared with experimental Q and spotted fevers, the enlargement of the spleen is, on the average, slighter. In early passages the spleen was in some guinea pigs three to four times its normal size, while in later trans-

3. *Fever charts of guinea pigs inoculated with human strain of Bullis fever isolated by Eight Service Command Laboratory Fort Sam Houston, Tex.*



fers twice enlarged spleens were not infrequently encountered. The parietal part of the peritoneum was sometimes injected and the abdominal cavity perhaps wetter than normal, although free, scanty, ascitic fluid was a rarity. The liver was found enlarged and dark in the first series but became normal in appearance in later transfers. A definite distention of the gall-bladder, sometimes accompanied by intense injection of its wall is a frequent phenomenon. Mesenteric glands were swollen and injected in guinea pig 1249 of the first passage, simultaneously with generalized lymphadenopathy. The adrenals were congested and usually swollen in most guinea pigs killed for transfers. Only in two instances testicles were slightly injected, particularly the polar fat. Cystitis was noticed

Table 4. Bullis Fever: Strain recovered from the tick Amblyomma americanum in guinea pig passages.

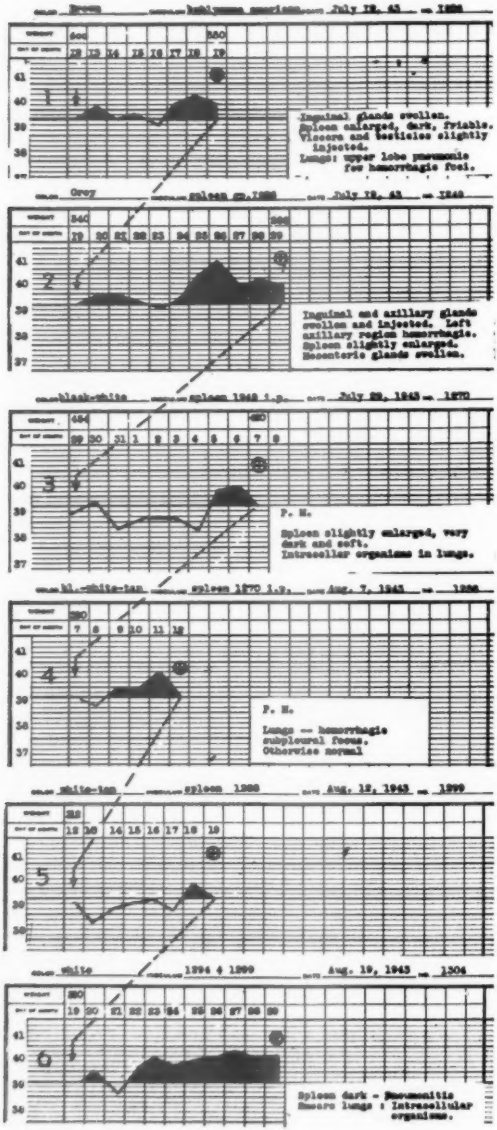
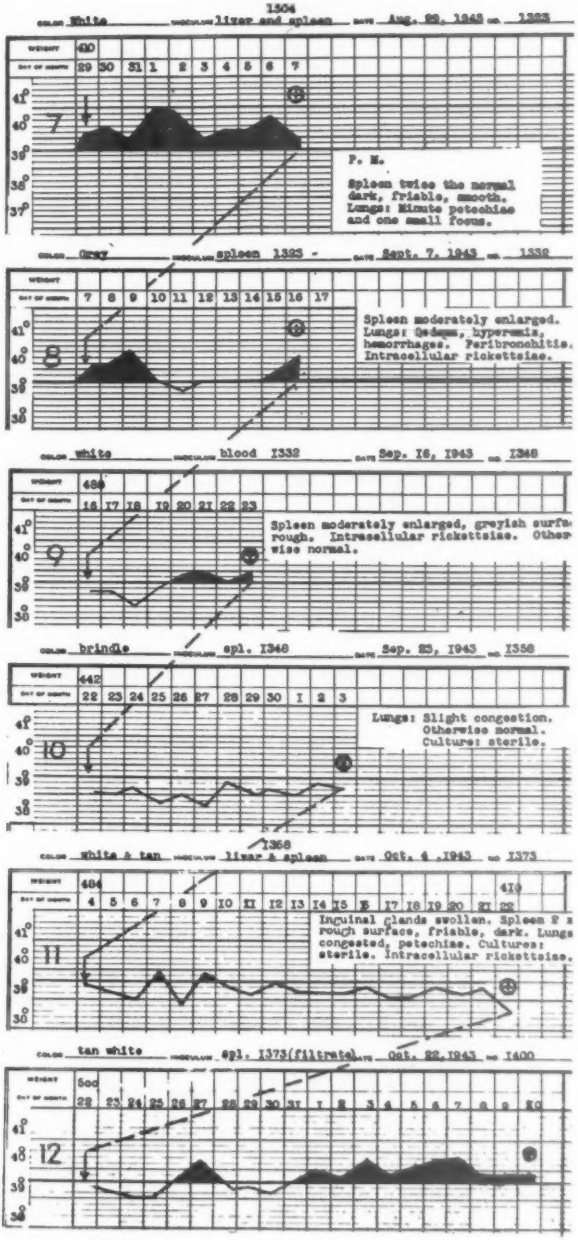


Table 4. (Cont.)

1504


COLOR White INOCULUM liver and spleen DATE Aug. 29, 1943 NO. 1383
WEIGHT 400
DAY OF MONTH 29 30 31 1 2 3 4 5 6 7
41° 40° 39° 38° 37°
7
P. M.
Spleen twice the normal dark, friable, smooth. Lungs: Minute petechiae and one small focus.
COLOR Gray INOCULUM spleen 1383 - DATE Sept. 7, 1943 NO. 1332
WEIGHT
DAY OF MONTH 7 8 9 10 11 12 13 14 15 16 17
41° 40° 39° 38°
8
Spleen moderately enlarged. Lungs: Oedema, hyperemia, hemorrhages. Peribronchitis. Intracellular rickettsiae.
COLOR White INOCULUM blood 1332 DATE Sep. 16, 1943 NO. 1348
WEIGHT 480
DAY OF MONTH 16 17 18 19 20 21 22 23
41° 40° 39° 38°
9
Spleen moderately enlarged, greyish surface rough. Intracellular rickettsiae. Otherwise normal.
COLOR brindle INOCULUM spl. 1348 DATE Sep. 25, 1943 NO. 1358
WEIGHT 442
DAY OF MONTH 22 23 24 25 26 27 28 29 30 1 2 3
41° 40° 39° 38°
10
Lungs: Slight congestion. Otherwise normal. Culture: sterile.
1358
COLOR white & tan INOCULUM liver & spleen DATE Oct. 4, 1943 NO. 1373
WEIGHT 404 410
DAY OF MONTH 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22
41° 40° 39° 38° 36°
11
Inguinal glands swollen. Spleen & rough surface, friable, dark. Lungs congested, petechiae. Cultures: sterile. Intracellular rickettsiae.
COLOR tan white INOCULUM spl. 1373(filtrate) DATE Oct. 22, 1943 NO. 1400
WEIGHT 500
DAY OF MONTH 22 23 24 25 26 27 28 29 30 31 1 2 3 4 5 6 7 8 9 10
41° 40° 39° 38° 36°
12

⊕ Killed.

in one case with petechial hemorrhages on the serosa of the bladder. The lungs usually showed injection of various intensity; in the majority of cases minute petechiae or small hemorrhagic circumscribed foci were noted on the pleural surface. No consolidation of lung tissue was, however, observed. Generally speaking, the condition of the lungs is in no way different from that of experimental spotted, typhus and Q fevers. The fatality rate among guinea pigs from the infectious agent is nil.

A histopathological study is so far in its preliminary stage. A hyperaemic condition of the spleen tissue with extravasation and hyperplasia of the folliculi was found in the few sections thus far examined. In the liver, round-cell infiltration of the bile ducts, indicating an inflammatory condition, constitutes the main lesion, probably responsible for bile retention. The lung tissue showed a general hyperaemia with infiltrations around the bronchi as well as focal infiltrations in the parenchyma with predominance of lymphoid cells. No "nodules" were seen in the brain but a thrombosis of the arteriolae and vascular proliferation was found in guinea pig 1304 (fifth passage) killed on the eighth day of high fever.

It is anticipated to supplement the above fragmentary observations on histopathology by a more systematic study. So far the study of the sections stained with Giemsa was primarily directed into the search of the specific agent.

In addition to guinea pigs, white mice of the Swiss strain were simultaneously inoculated with tick emulsion by the intraperitoneal and intranasal routes. No visible effect was noted in mice for the first three weeks, after which time the mice began to die showing almost in all cases a conspicuous splenomegaly. Some of the spleens were greatly enlarged—about five to six times. This condition was observed also in mice inoculated intranasally without any visible changes in the lungs.

Several large spleens of mice originally inoculated with *Amblyomma americanum* were emulsified, pooled and passed into two guinea pigs, both of which developed fever on the sixth day. One of them was killed on the fourth day of fever and its spleen used for further passages. Bac-

teriological tests of the enlarged spleen of this guinea pig showed sterility.

It was at this stage of our work when we were able to compare our preliminary results with those obtained by the Eighth Service Command Laboratory at Fort Sam Houston, Texas, on the agent isolated directly from the blood of Bullis fever patients. Although a comparison of our experimental disease in guinea pigs and mice showed a close similarity if not identity, for the final conclusions immunity tests had to be carried out.

C. Immunity tests.

For this purpose 23 guinea pigs after recovery from our agent of tick origin were sent to Fort Sam Houston. The guinea pigs were divided in two groups—eleven tested against two strains isolated from Bullis fever patients by Colonel Livesay and Captain Pollard, while the second group of twelve animals was challenged with spotted fever. Out of the eleven test guinea pigs, ten showed complete immunity to the human strain of Bullis fever, while one only remained susceptible. Of eleven control animals nine developed fevers while two did not react. Of the twelve test guinea pigs exposed to spotted fever infection only one failed to react; it also failed previously to react to the inoculation with our strain of tick origin. These results showing lack of immunity to spotted fever stay in agreement with our previously made tests.

The above experiments are of significance as they throw light on the close relationship if not identity of the infectious agent isolated by us from *Amblyomma americanum* from Camp Bullis with the strain recovered by Livesay and Pollard (1943) from blood of Bullis fever patients.

Furthermore, evidence has been brought forward by the present work that the tick *Amblyomma americanum* is the actual carrier of Bullis fever as anticipated by Woodland, McDowell and Richards (1943). Since it was found by Parker and Kohls (1943) that *Amblyomma americanum* is also a carrier of Q fever rickettsiae in Texas our strain was tested at the suggestion of Dr. R. R. Parker against American Q fever. The Q fever strain originally isolated by the Rocky Mountain Laboratory from *Dermacentor andersoni* of Wyoming was kindly supplied by Dr. Parker. In our experience normal guinea pigs react to either intraperitoneal or

subcutaneous infection with this "hot" strain with high fever ranging between 40° and 41° C. for six to seven days.

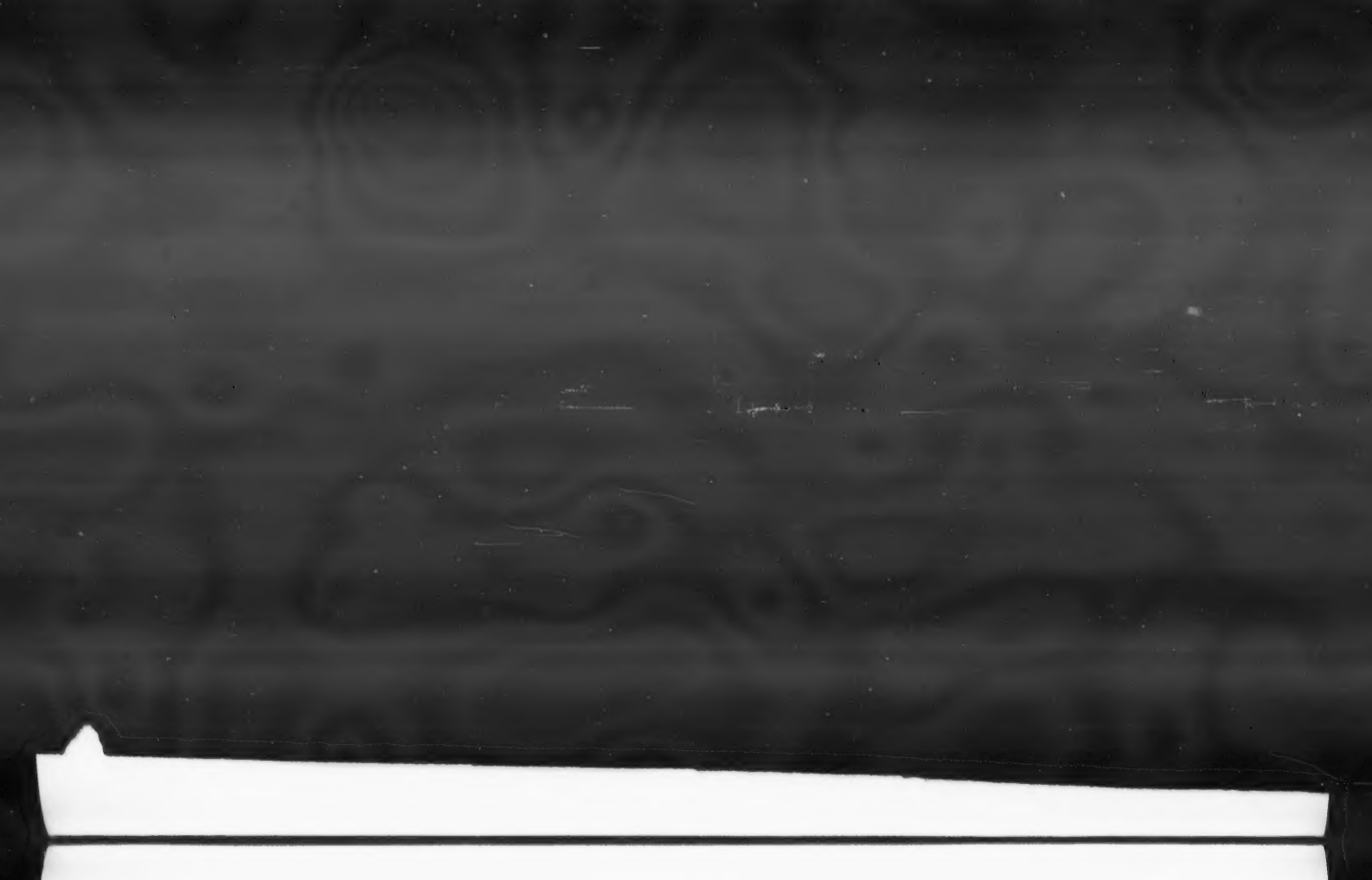
For immunity tests a series of seven guinea pigs convalescent from our Bullis fever strain were reinfected with Q fever with the result that six animals developed Q fever of the same intensity as the four controls. Only one guinea pig of the test series which had failed to react to the Bullis strain remained immune to Q fever. These experiments show so far that there is no relationship between our Bullis fever strain of tick origin and Q fever. This agrees with the negative serological tests on Bullis fever patients for Q fever (Woodland, McDowell and Richards, 1943).

DEMONSTRATION OF RICKETTSIAE

Practically all the experimental animals (guinea pigs and white mice) when killed for passage were tested for bacteriological sterility. As a routine, fragments of the spleen, lungs or liver were inoculated into nutrient broth simultaneously with the passages. In addition, heart-blood from passage guinea pigs was in some instances tested for sterility. At the beginning, our work was greatly handicapped by an accidental Pasteurella infection of our spotted fever strain kept in guinea pigs but due to drasitc measures taken, i. e. destruction of all the animals involved, the spread of the infection was prevented.

The examination of the organs for microorganisms was carried out in smears and sections from lungs, spleen and liver. Impression smears were stained with Giemsa for 30 minutes while the organs after fixation in Regaud solution were stained with Giemsa for 24 hours and then differentiated and treated after Wolbach's method.

The first demonstration of microorganisms was successful in smears of lungs from a guinea pig of the first series inoculated with tick emulsion. This guinea pig (1217) developed high continuous fever after five days of incubation and was killed on the fifth day of fever. The spleen was found 3-4 times enlarged, dark, friable, its surface smooth. Inguinal glands were swollen, not injected. Adrenals were injected and had haemorrhagic foci. Lungs were found congested and showed minute petechiae on the pleural surface. Blood and lung cultures were found sterile after 72 hours of incubation.



Smears from lungs of this guinea pig showed in several large mononuclear cells purplish red stained minute coccoid organisms single or diplococcal scattered in the cytoplasm. (Figure 1, a, b, c, d.) They were found in various numbers and size; some of the cells contained about 20 organisms while in others more than 50 could be differentiated. Some of the organisms were on the borderline of visibility in contrast to others of the size of a micrococcus. In addition to the large mononuclear cells, similar organisms were found in lymphocytes. Minute extracellular bodies of the same staining properties but more uniform in size were found in smears from lungs and spleen. In the above described case the organisms were comparatively scanty in number; in further passages, however, they appeared more numerous. A mass invasion of some large mononuclear cells was noted in guinea pig 1314 of the fifth passage, which after running an irregular fever was killed on the twelfth day of disease with signs of pneumonitis. In smears stained with Giemsa dense masses of purplish red organisms were observed in the cytoplasm at one pole of some of the large mononuclears. Two morphological types of organisms could be distinguished, the predominant being slender and delicate bacilli, clumped together, and among them coccoid bodies (Figure 1, e). Besides, single coccoids were scattered in the cytoplasm, similar to those described above.

In fact, the above described intracellular pleomorphic organisms, their accumulations resembling "microcolonies" as well as their staining properties bear a striking similarity with rickettsiae. Very similar observations were made in lung smears from a guinea pig of the sixth passage, in which the intracellular organisms were uniformly coccoid in shape. As can be seen from the photomicrograph (Figure 2) one of the organisms situated extracellularly shows bipolar staining which structure represents another characteristic aspect of rickettsiae. Intracellular organisms could also be demonstrated in sections of the liver (guinea pig 1304) of the fifth passage. There, within the inflammatory focus some of the infiltrating cells surrounding the bile duct were found filled with minute coccoid organisms. (Figure 3.) Characteristic findings were also observed in guinea pig 1348 of the eighth passage, and killed on the fourth day of low fever. These intracellular organisms, mostly coccoid

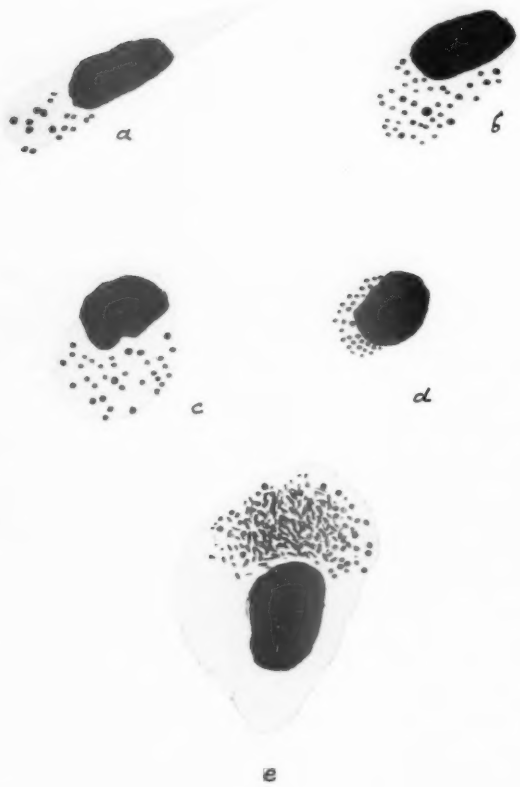


Figure 1. Rickettsiae-like organisms in lung smears of guinea pigs infected with Bullis fever agent of tick origin. Giemsa stain. Approximately 1200 x.

in shape are apparently different in size, but the larger, somewhat irregularly shaped bodies may be interpreted as agglomerations of the smaller single elements. (Figure 4.)

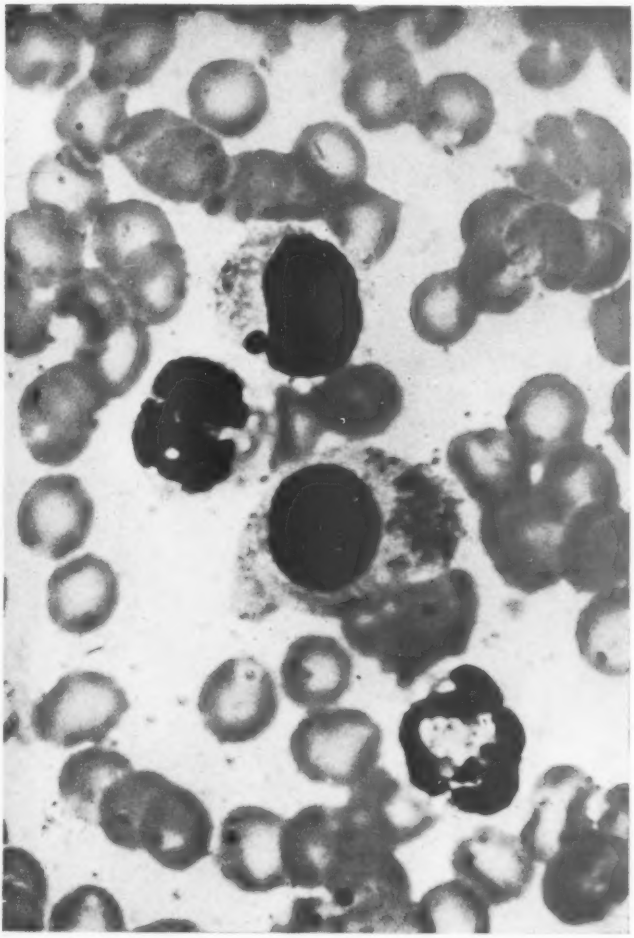


Figure 2. Intracytoplasmic rickettsiae in a large monuclear cell. Impression-smear from lung tissue of guinea pig 1322 (sixth passage). Giemsa stain. Approximately 1500 x.

The above findings were observed in transfer guinea pigs killed during various stages of fever. As mentioned

above blind passages from afebrile guinea pigs were also made in order to keep the strain going. In these subclinical cases in which the disease could only be revealed

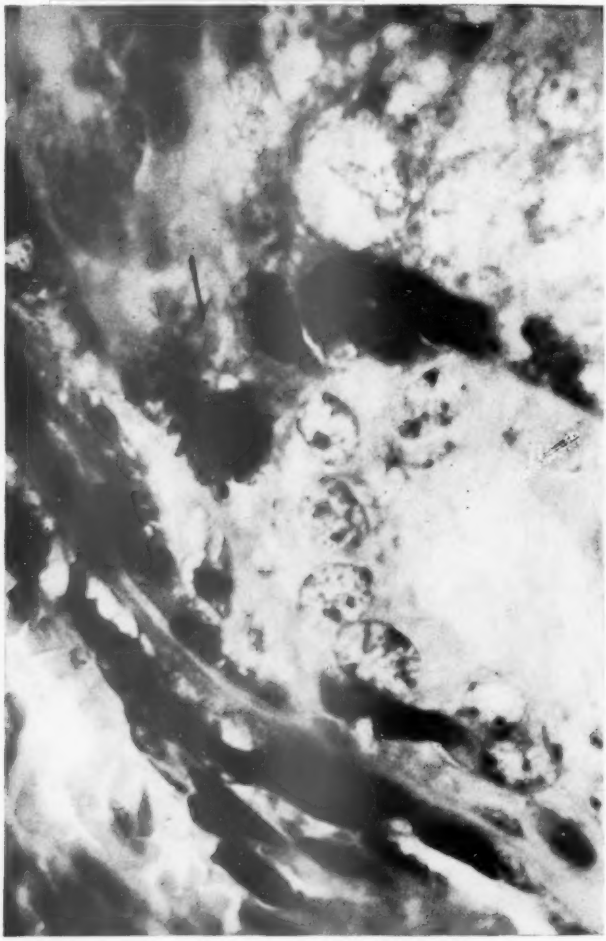


Figure 3. Section of the liver of guinea pig 1304 (fifth passage) showing intracytoplasmic rickettsiae in a lymphoid cell. Approximately 900 x.

by pathological lesions (enlarged spleen and pneumonitis) the detection of rickettsiae was obviously of high diagnostic value. This was the case in guinea pig 1357 of the

ninth passage which after inoculation with the spleen of guinea pig 1348 (Figure 4) remained afebrile during fourteen days of observation. It was then killed showing a

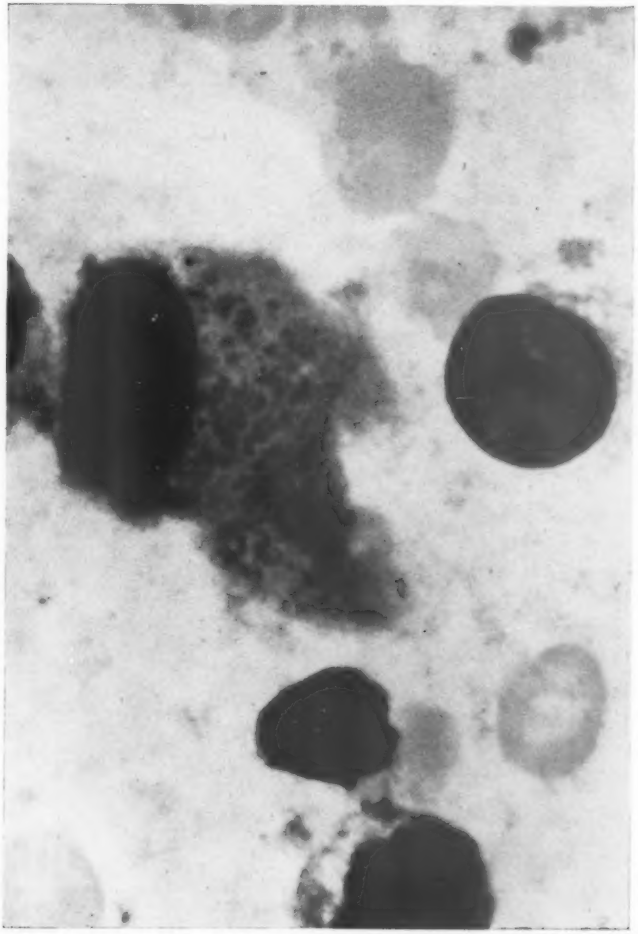


Figure 4. Intracellular rickettsiae in liver impression-smear of guinea pig 1348 (eighth passage). Giemsa stain. Approximately 2000 x.

slightly enlarged spleen, a discrete mottling of the liver and petechiae on the pleural surface of the lungs. In the smears of the lung tissue intra- and extracellular rickett-

siae were found. There was a mass invasion of few mononuclear cells, with accumulation of coccoid rickettsiae in the cytoplasm close to the nucleus (Figure 5). Other rickettsiae probably originating from ruptured cells were scat-

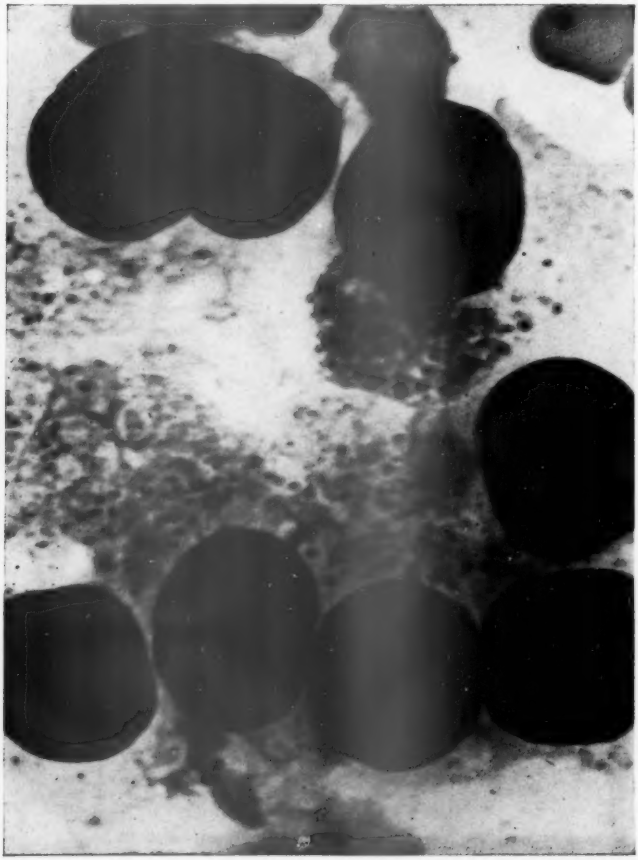
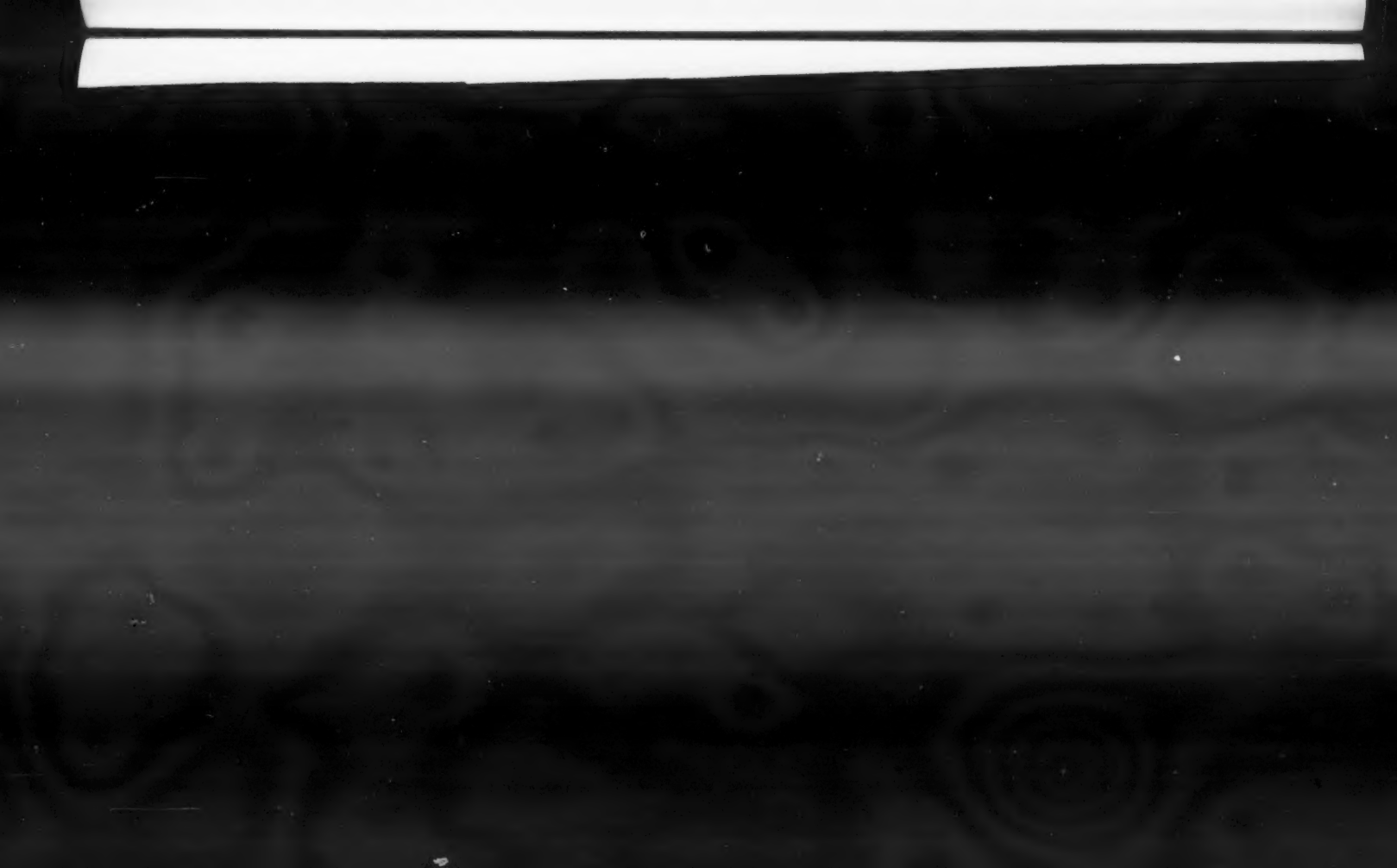


Figure 5. Smear of lung tissue of guinea pig No. 1357 (ninth passage) showing intracytoplasmic rickettsiae close to the nucleus. Also numerous extracellular rickettsiae. Giemsa stain—2000 times.

tered over the field and were also found in close vicinity to the nuclei (Figure 5). In studying the aspect of the rickettsiae, particularly their location and characteristic grouping,



one cannot fail to note the extreme similarity with the rickettsiae of tsutsugamushi. This similarity becomes impressive when Figure 5 is compared with Figure 9 of Lewthwaite's and Savoor (1936) studies on tsutsugamushi. No further conclusions can be drawn, however, from these morphologic observations except that the latter might perhaps supplement our previous remarks as to the apparent clinical resemblance of Bullis fever with tsutsugamushi.

The fact that our strain originated from one hundred pooled ticks collected at random from the epidemic area shows that at least one of them was infected with the Bullis fever agent. Should this be the average index it would indicate that the infectivity rate of *A. americanum* is in this case unusually high. This probability can be supported by the sharp case incidence of Bullis fever during the months of April, May and June when the activity of ticks is at its height.

The present experimental study, which is still in progress, thus demonstrates that *A. americanum*, a carrier of spotted and Q fevers, is also a vector of another human rickettsiosis—Bullis fever.

SUMMARY

An infectious agent, not cultivable on ordinary bacteriological media, has been recovered from guinea pigs inoculated with ticks *(Amblyomma americanum)* collected from the military reservation area—Camp Bullis, Texas. The place of origin of the ticks has been for the last two years the scene of mass outbreaks of an apparently new clinical syndrome, called Bullis fever, and first described by Woodland, McDowell and Richards (1943).

The infection causes in guinea pigs a disease characterized by fever of various types among which an attack of short duration after an incubation period of nine to twelve days deserves attention. Continuous fever and relapses of short duration were also observed.

The gross pathology in guinea pigs is dominated by splenomegaly and generalized lymphadenopathy but only in early passages of the infection from ticks. White mice (Swiss strain) infected with this agent also show splenomegaly. The above symptomatology and pathological lesions correspond to the experimental disease produced by the in-

fectious agent isolated from human cases of Bullis fever (Livesay and Pollard, 1943). Furthermore, guinea pigs convalescent from the infection originating from ticks proved immune to the Bullis fever strain of human origin.

No immunological relationship between our strain and either spotted fever or Q fever was found.

An intracellular organism was demonstrated in smears and sections from organs of infected guinea pigs. The morphological and biological properties of this organism, including its transmission by an arthropod, correspond to the features of pathogenic rickettsiae.

The results of the present work also demonstrate that *Amblyomma americanum* is the vector or at least one of the carriers of Bullis fever in nature.

ACKNOWLEDGEMENTS

The writers wish to express their gratitude to Colonel Harvey R. Livesay, M. C., Commanding Officer, Eighth Service Command Laboratory, and to Captain Morris Pollard, V. C., for their valuable assistance particularly in the performance of the immunity tests.

The assistance of Dr. James M. Brennan, Post Surgeon's Office, Fort Sam Houston, Texas, in the identification and the supply of ticks is greatly appreciated.

The present work derived great benefit from the authoritative advice and suggestions of Dr. R. R. Parker, Director, Rocky Mountain Laboratory, U. S. P. H. S.

These investigations were greatly facilitated by the stimulating interest and support of Dr. Chauncey D. Leake, Dean, and of Dr. Carl A. Nau, Chairman of this Department.

The histopathological studies greatly benefited from consultations with Dr. Paul Brindley, Chairman, Dept. of Pathology, and were assisted by the expert help of Miss Beryl Brewer, Chief Technologist.

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EVANGELISTA TORRICELLI AND THE BAROMETER

Among the many centennials of important scientific events which might have been celebrated this year, had it been more peaceful, is the tercentennial of the discovery of the principle of the barometer in 1643 by Evangelista Torricelli (1608-1647). This discovery ranks in importance with the publication a century earlier of the *De revolutionibus orbium coelestium* of Nicolaus Copernicus (1473-1453), which established modern astronomy, and the *De humani corporis fabrica libri septem* of Andreas Vesalius (1514-1564), which established modern anatomy. For, Toricelli's barometer established modern meteorology.

Evangelista Torricelli was born in Faenza, and, orphaned early, was sent to Rome to study mathematics at the Papal College. Profoundly influenced by Galileo, he moved to Florence in 1641 and became Galileo's secretary. On Galileo's death, Torricelli became professor of mathematics in the Florentine Academy.

The weight of the air was first appreciated by Torricelli in filling a long tube sealed at one end, with mercury, inverting it, and putting it in a bowl of mercury. The liquid in the tube fell to a distance varying between 29 and 31 inches, in a manner which indicated a relationship to climatic change.

Since the famous Hippocratic writing, *on airs, waters and places*, physicians have appreciated the influence of climatic variations on disease. The scientific study of these relationships was made possible by the systematic survey of climate, the most important instrument for which is the barometer. Less than a hundred years ago, James Blake (1815-1893), the brilliant English founder of modern pharmacology, who had emigrated to this country, established the principles of the "polar front" which are at the basis of modern meteorology. William F. Petersen's remarkable studies (recently culminating in his *Lincoln-Douglas: The Weather as Destiny*, C. C. Thomas, Springfield, Illinois, 1943) afford some idea of current interest in the problem. Perhaps a systematic institute investigation of the matter, as part of a school of geographic medicine, would reveal some startling information, as a result of which Torricelli's barometer might acquire even greater significance than it now has.

C. D. L.

ALBINO DEER MICE (*PEROMYSCUS MANICULATUS GAMBELI*) AS AN IDEAL SUSCEPTIBLE TEST ANIMAL FOR STUDYING WEIL'S DISEASE*

A. PACKCHANIAN**

In a previous study, the writer has demonstrated the resistance of six and the susceptibility of 25 species and subspecies of American rodents to *Leptospira icterohaemorrhagiae* (7). The object of the present communication is to give additional data and to point out the extreme susceptibility of which albino deer mice (*Peromyscus maniculatus gambeli*) exhibit to *Leptospira* (6, 8).

METHODS AND MATERIALS

The origin and the stock supply of albino deer mice (*Peromyscus maniculatus gambeli*) : Two white *P. m. gambeli* were first noted by Sumner in 1919 in a brood. Their parents were sibs belonging to the first cage-born (C_1) generation. They had six normally colored offspring, one of which proved to be heterozygous for albinism. From this original stock an indefinite number of albino descendants were reared. The albinism of this strain is typical and complete; genetically, it is a simple recessive (9). The strain of albino deer mice (*P. m. gambeli*) was sent by Dr. F. B. Sumner from California to Dr. Lee Dice, at the University of Michigan, during 1925 (2). The writer obtained several pairs of the breeding stock from Dr. Lee Dice and his former associate, Dr. H. Feldman, during 1929 (3) and has since maintained this strain in the laboratory. The strain thus far has proved to be prolific, a fertile female usually gives birth to a brood of four to five offspring each month. Their food consists of Purina dog chow and water, occasionally carrots (1, 2). The animals were reared in wire cages which are a slight modification of the cages in use at the University of Michigan.

*From the Division of Parasitology and Tropical Medicine Laboratory Service, McCloskey General Hospital, United States Army, Temple, Texas. A part of this study was performed in the School of Medicine, University of Texas, and in the National Institute of Health, United States Public Health Service, Washington, D. C., during 1936-1942. Received for publication March 3, 1943.

**On leave-of-absence from the School of Medicine, University of Texas, Galveston.

The strains of Leptospira icterohaemorrhagiae: The original source and the history of various strains of *Leptospira* isolated from man, rats, and dogs have been described in previous publications (4, 5). Most of these strains have been used from time to time in connection with the present study. A strain of *Leptospira* isolated from a rat in 1938, virulent to deer mice, has been maintained *in vitro*. After three years *in vitro* cultivation, the strain was retested for its relative virulence for guinea pigs and albino deer mice (*P. m. gambeli*).

The inoculum and the mode of inoculation: Whenever few mice were inoculated, the inoculum consisted of one or two drops of infectious blood obtained from the ear of a guinea pig or from the tail of a deer mouse, which blood was suspended in about 0.5 c.c. physiological salt solution. When more than ten deer mice and other animals were used in a given experiment, the inoculum was prepared by removing about 5.0 c.c. of infectious blood from a guinea pig, defibrinated, and suspended in an equal volume of physiological salt solution.

In some instances, the source of *Leptospira* was the scrapings from the surface of the cortex of the kidneys of naturally or experimentally infected rats (*Rattus norvegicus*) and house mice (*Mus musculus*).

In a few experiments, the urine of experimentally infected deer mice (*P. m. gambeli*) obtained just before death or immediately after the death of the animal was used as an inoculum.

Occasionally virulent and slightly virulent cultures of *Leptospira* were also used; such cultures invariably contained over a million spirochetes per cubic centimeter.

Each animal was inoculated with 0.2 to 0.3 c.c. of a suspension of infectious blood or culture, intraperitoneally or subcutaneously.

Examination of inoculated animals: Following the inoculation, the deer mice were placed in suitable glass jars and observed daily for evidence of infection.

Droplets of blood obtained from the tail of each deer mouse were examined by darkfield illumination for *Leptospira* (high dry objective 45X, Ocular 10X, and with oil immersion lens 91X, Ocular 10X).

All the animals were observed for the development of the "external" jaundice in the ears, feet, toes, and sclerae. In some deer mice bloody urine and loss in weight was noted and recorded.

At the autopsy, search was made for microscopic jaundice and haemorrhage in the skin, subcutaneous tissues,

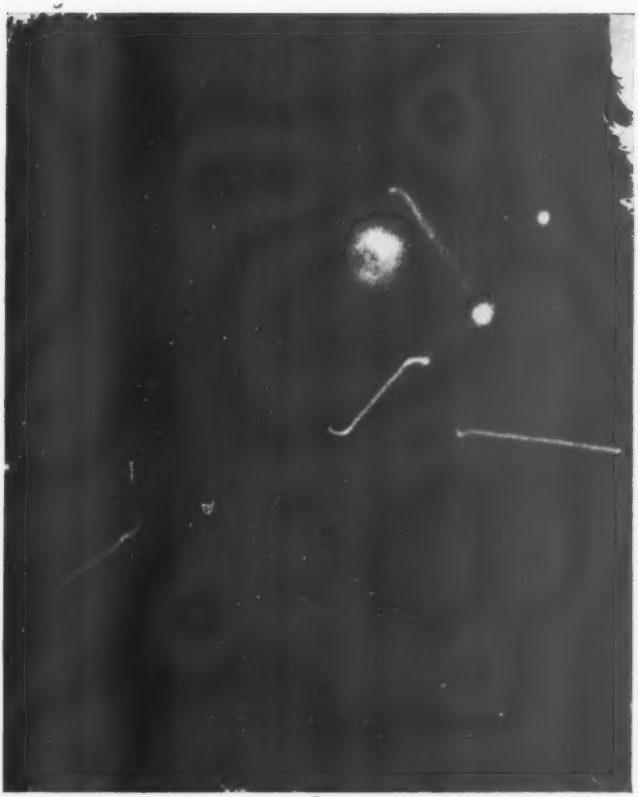

Figure 2. Leptospira icterohaemorrhagiae from a culture. Dark-field illumination.

muscles and in the thoracic and abdominal cavities. Sections taken from organs were fixed in 10 per cent formaldehyde and stained with Levaditi's or Warthin's method.*

*The writer wishes to express his appreciation to Dr. R. D. Little and L. L. Ashburn at the National Institute of Health, for their cooperation in the histopathological studies.

EXPERIMENTAL DATA

The virulence and the fatality of Leptosipar icterohaemorrhagiae to albino deer mice (Peromyscus maniculatus gambeli) : Over 400 albino deer mice (*P. m. gambeli*) inoculated with special strains of virulent *Leptospira* all died with icterohaemorrhagic spirochetosis within 15 days. The majority of these animals died on the fourth or fifth day of illness.

This species of American deer mice was found equally susceptible to various serological types of *Leptospira* (I, II, III, IV), which included strains isolated directly from man, dogs and rats.

Whenever a strain of *Leptospira* was infective to guinea pigs, it always produced infection in albino deer mice which terminated fatally within about a week.

When a strain of *Leptospira* (Type I) isolated directly from the kidney scrapings of naturally infected rats (*Rattus norvegicus*) was inoculated into several albino deer mice and two guinea pigs, all animals contracted the disease and died with icterohaemorrhagic spirochetosis, the deer mice within six days and the guinea pigs within ten to fourteen days. This strain was isolated *in vitro* and after three years subcultviation at irregular intervals albino deer mice and guinea pigs were inoculated with the culture. The albino deer mice contracted the infection and died with icterohaemorrhagic spirochetosis, while the guinea pigs survived.

With less virulent strains of *Leptospira* the mortality rate was somewhat lower, and occasionally a few deer mice survived. The heart blood removed from such animals a few months following the inoculation of the animals and specific agglutinins for *Leptospira* were found present in the sera in significantly high dilutions (1:10,000).

A few strains of *Leptospira* were maintained *in vivo* by syringe passage in deer mice (*P. m. gambeli*). The blood from the tail of the animal at the height of the infection or the heart blood at autopsy was used as inoculum. By such a procedure the strain of *Leptospira* for deer mice was exalted and reached the so-called "virus fixed" stage in about three days.

The strains of *Leptospira* from experimentally infected deer mice were readily cultured *in vitro* on liquid and semisolid media. Such strains have been sub-cultured for many generations, growing readily and luxuriantly.

In general, experimental Weil's disease in albino deer mice ran an acute course, characterized by the invasion of the blood stream with *Leptospira*. The microorganism appeared in the circulating blood within 48 hours; their number increased rapidly and in four to six days the blood of the animal was found swarming with spirochetes. One or two days before death of the animals, external jaundice developed, as noted particularly on the ears, feet and sclerae of the eyes.

The findings at autopsy immediately after the death of the animals revealed marked jaundice and haemorrhages. (See Fig. 1). The petechia and yellow discoloration of the skin and subcutaneous tissues were present in a majority of cases. The hemorrhages were found to be present in any given organ, tissues or cavities; such as in the subcutaneous tissues in the intestines, in the plural and abdominal cavities.

Histopathological studies revealed numerous *Leptospira* in the section from organs and tissues. *Leptospira* were abundant in the liver, much less numerous in the kidney and were found in the heart and lungs in very small number. The spirochetes took a dark brown, almost black, color with silver stain. The *Leptospira* present in the liver sections were so numerous that the spirochetes overlaid one another and formed "garlands" around the separated liver cells; the organism was not found within the liver cells. (See Fig No. 3).

Other pathological alterations consisted of enlargement of the liver cells, increase in the number of nuclei per cell, swelling and oxyphilia of some Kupffer cells, necrosis of an occasional parenchymal cell, and disruption of the liver cells due to loss of cohesion between cells. Erythrophagia was present in liver and in spleen, more frequently and prominent in the spleen. The kidney cortex, mainly the inner portion, showed changes in the tubular epithelium, including cytoplasmic swelling, adhesion between cells and focal necrosis.

Figure 1. American deer mice (Peromyscus maniculatus gambeli). (a) Animal expired five days after inoculation with a virulent strain of Leptospira icterohaemorrhage. Note the jaundice and hemorrhages. (b) Control.

Evidence of bile pigments, yellow pigmentation of some cells, large and small hemorrhagic emboli and focal hemorrhages and marked congestion were encountered in these sections.

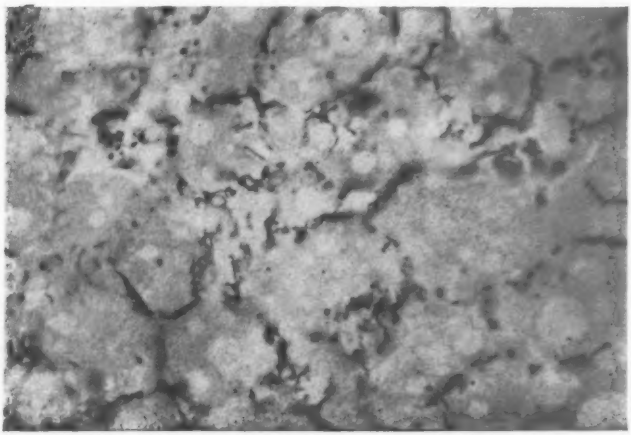

Figure 3. Leptospira icterohaemorrhagiae in a tissue section from a deer mouse, which died with leptospirosis. Levaditi's stain, magnification 1650X.

DISCUSSION

> "The happy choice of an animal, an instrument constructed in some special way, one reagent used instead of another, may often suffice to solve the most abstract and lofty question." —Claude Bernard.

The fact that several species of American deer mice extremely susceptible to *Leptospira icterohaemorrhagiae* suggests the desirability of utilizing these animals for diagnostic and experimental studies of Weil's disease (leptospirosis.) Although 26 species and subspecies of rodents are equally susceptible to *Leptospira*, it seems important to select a species that can be used by most workers, such a choice will aid in the uniformity of the results of various investigators and will simplify the problems of the animal dealers who would rear one or two species of deer mice instead of many.

Taking all data into consideration, it appears that albino deer mice (*P. m. gambeli*) is the animal of choice for the following reasons:

1. The albino deer mice (*P. m. gambeli*) are very susceptible to virulent strains of *Leptospira*, and will die from the disease in three to seven days.

2. *Leptospira* usually are present in the circulating blood of albino deer mice before the second day after the inoculation, their number increases rapidly and at the height of infection the blood will be found swarming with *Leptospira*.

3. External jaundice is more readily detecable in albino deer mice (*P. m. gambeli*) than in other susceptible species of deer mice.

4. Because of the small size of deer mice, they can be kept in glass jars, thus confining the infective excretions.

5. The gross and microscopic pathology, as found in albino deer mice (*P. m. gambeli*) is characteristic and diagnostic for Weil's disease.

In addition, a supply of albino deer mice in certain laboratories is desirable because this species of deer mice is an ideal animal in which to keep the stock of pathogenic trypanosomes, such as *Trypanosoma brucei, T. evansi,* and others, for class-room demonstration and for research purposes (3, 4, 5).

For the diagnostic study of Weil's disease (leptospirosis), samples of blood and urine from humans and from dogs suspected of having Weil's disease should be inoculated into three to four albino deer mice (*P. m. gambeli*) and two young guinea pigs and into suitable culture media. (The inoculation of the animals with patient's blood or urine, or both, should be done in the very early stage of the disease). Deer mice will die within a week and guinea pigs within two weeks if virulent *Leptospira* are present in the inoculum. When an inoculated animal fails to die and *Leptospira* are not demonstrable in its blood at the end of the fourth week, the heart blood of the animal should be removed and tested for the presence of agglutinins and lysins (6, 8). Whenever it is desirable to demonstrate *Leptospira* in the tissues as a further diagnostic aid, a portion of the liver and kidneys should be removed at

autopsy and fixed in 10 per cent formaldehyde and sections stained with Levaditi's or Warthin's method for spirochetes.

It is noteworthy that regular laboratory white mice (*Mus musculus*) usually do not die when inoculated with virulent strains of *Leptospira*, nor do they manifest any external jaundice or hemorrhages. These mice, when inoculated with *Leptospira*, contract an abortive infection of the blood as do house rats (*Rattus norvegicus*) and become chronic carriers. The *Leptospira* are usually present in the kidneys of these animals, and some of the organisms are periodically eliminated in the urine. These findings are in distinct contrast to those found in the albino deer mice (*P. m. gambeli*), which are extremely susceptible to *Leptospira* and dies of the infection within seven to ten days (5, 6). It is an interesting fact that the converse is true in the case of experimental *Trypanosoma brucei* infections. With this microorganism, ordinary laboratory white mice (*Mus musculus*) contract an acute infection and die by trypanosomiasis within a week, while albino deer mice (*P. m. gambeli*) contract sub-acute infections and survive the disease for as long as three or more months with manifestations of trypanolytic relapses and crises (3, 4, 5).

SUMMARY

The albino deer mouse (*Peromyscus maniculatus gambeli*) is an ideal laboratory test animal for the diagnosis of Weil's disease and for studying experimental leptospirosis. (a) The duration of the illness in deer mice is short, terminating fatally in one week. (b) *Leptospira* can be demonstrated in the peripheral blood of deer mice in large numbers. (c) Because of the small size of the animals, they can be placed in glass jars, thus confining the infective excretions. (d) The gross and microscopic pathology found present in albino deer mice are confirmatory for Weil's disease.

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CALLING ATTENTION TO: ITEMS OF POSSIBLE INTEREST TO FRIENDS OF OUR EFFORT

OCTOBER, 1943

1. **Henry Schuman Hits the Bulls-Eye:** With Harvey Cushing's **Bio-bibliography of Andreas Vesalius,** prefaced by John Fulton, having 83 illustrations, costing $15; John Fulton's description of the **Harvey Cushing Collection of Books & Mss.,** at $8½; G. Rosen's **History of Miner's Disease,** prefaced by Henry Sigerist, costing $8½, & Henry Sigerist's translation of **Arnold of Villanova's Treatise on Wine,** costing $10.

2. **More books:** Eliel Saarinen's **The City: Its Growth: Its Decay: Its Future** (Reinhold, New York, 1943) skillfully compares a city to the growth of any organism, which if uncontrolled gets cancerous & centrally necrotic. P. de Kruif's **Kaiser Wakes the Doctors** (Harcourt, Brace, N. Y., 1943) may be overenthusiastic, but it's interesting. Oxford announces 2nd ed. of John Fulton's **Physiology of the Nervous System** ($9). Sure to be good is E. V. Cowdry's **Microscopic Technique in Biology & Medicine,** and W. Truslow's **Body Poise** (Wms. & Wilkins, Balt.). Princeton Press offers C. E. A. Winslow's **Conquest of Epidemic Diseases: A Chapter in the History of Ideas.** The Office of Scientific Research & Development will send mimeo of R. A. Phillips, D. D. Van Slyke & Co.'s **Copper Sulfate Method of Measuring Specific Gravities of Whole Blood & Plasma.** Winthrop Chemical Co. will send bibliography on penicillin.

3. **Endocrines:** F. L. Dey (Endocrin., 33: 75, 1943) notes that hypothalmic lesions prevent hypophyseal secretion of luteinizing hormone, resulting in genital hypertrophy. K. J. Karnaky (**Journ. Clin. Endocrin.,** 3: 413, 1943) finds hexestrol less toxic but less potent than diethylstilbestrol, while J. G. Crotty & Co. (**Surg. Gyn., Obs.,** 77: 130, 1943) thinks hexestrol is best for estrogenic therapy. More evidence supporting treatment of tumors by estrogens is given by W. M. Biden (**Brit. Med. J.,** 2: 57, 1943) & G. H. Duncan (**Ibid.,** p. 137). K. N. Krishman finds that anterior pituitary extract (Antuitrin-G) promotes calcium retention (**Indian Journal Med. Res.,** 30: 589, 1942). H. E. MacDermot describes fine McGill mural on endocrines by Marian Scott—like Homer Wheelon's (**Canad. Med. Asso. J.,** 47: 224, 1943).

4. **Chemotherapy:** H. L. Chung & H. K. Chow (**Chinese Med. J.,** 61: 71, 1942) find new sodium salt of mannite antimonic acid very effective in experimental kala-azar, but with some kidney and liver injury. The **Chinese Medical Journ.** now is published from Washington, D. C. A. I. Permer & A. I. Bernheim (**Gastroenterol.,** 1: 1765, 1943) note that ergotamine tartrate inhibits hemoconcentration & anatomical lesions in alimentary tract due to Shiga toxin. Q. B. Lee (**Texas State J. Med.,** 39: 175, 1943) finds sulfanilamide locally significantly reduces mortality & morbidity in appendicitis. H. E. Carter & S. R. Dickman find anomalous amino nitrogen values in penicillin suggesting caution; doubt presence of free primary animo group in penicillin (**J. Biol. Chem.,** 149: 571, 1943). Another question—does penicillin contain sul-

fur? Funny if it were to be relatively simple "enzyme" or "vitamin" competitor. F. Bernheim and H. I. Kohn (**Science**, 98: 223, Sept. 3, 1943) show propamidine (4:4 diamidino-diphenoxy propane) to be more powerful bacterial inhibitor than stilbamidine & to act by inhibiting cellular oxidative metabolism.

5. **Etc.**: J. P. Muzzo (**Rev. Med. Exp.**, Lima, 2: 25, 1943) finds overproduction of fibrinogen in anemias of interesting Carrion's disease (C. Howe **Arch. Int. Med.**, 72: 147, 1943; **Sci. Month**, Aug., 1943). L. Pauling & Co. (**Science**, 98: 263, Sept. 17, 1943) confirm J. R. Marrack's framework of lattice theory of serological precipitation & agglutination (**Chemistry of Antigens & Antibodies**, Med. Res. Counc., London, Report No. 230, 1938). J. H. Quastel offers neat survey of enzymes & their mode of action (**Endeavor**, 2: 85, 1943). A. Weil (**Growth**, 7: 257, 1942) finds male rat brain matures chemically earlier than female—with aging there is increase of lecithins, galactolipids & sphyngomyelins at expense of cephalin. W. Blackwood & H. Russell (**Edin. Med. J.**, 50: 385, 1943) find prolonged nerve muscle injury in experimental immersion foot. Thorough study of toxicity of tannic acid by G. R. Cameron & Co., in **Lancet** (Aug. 14, p. 179, & Aug. 21, pp. 218, 222, 1943).

NOVEMBER, 1943

1. **Provocative**: E. G. Conklin's **Man: Real and Ideal** (Scribner's, New York, 1943) offers challenging observations and reflections on man's nature, development and destiny, scientifically sound and artistically offered. H. E. Sigerist discusses the University's dilemma (**Bull. Hist. Med.**, 14: 1, 1943) in facing the dangers to research. How about the danger of a scientific canon developed through control of the scientific journals by prejudiced editors?

2. **Psychiatry**: W. A. Bryan discusses **Administrative Psychiatry** (Norton, New York, 1943). A. Deutsch present a history of the **Mentally Ill in America** (Doubleday, New York, 1943). Not as good as G. Zilboorg's **History of Medical Psychology** (Norton, New York, 1941) is J. K. Winkler's **Mind Explorers** (Reynal, New York, 1943). S. S. Tompkins edits a reprint collection on **Contemporary Psychopathology** (Harvard, 1943). Harvard also publishes S. Cobb's excellent **Borderlands of Psychiatry**. O. S. English and G. H. J. Pearson discuss **Common Neuroses of Children and Adults** (Norton, New York, 1943). H. R. Love offers an excellent summary on dyspeptic symptoms in soldiers **Med. J. Australia**, 2: 101, Aug. 7, 1943), showing that appropriate man management may reduce symptoms in two-thirds.

3. **Historical**: M. F. Montagu discusses Edward Tyson (1650-1708) and the rise of human anatomy in England (**Mem. Amer. Philo. Soc.**, 20: 1-476, 1943). Interesting series of discussions on the early history of science and learning in America is sponsored by the American Philosophical Society (**Proc.**, 81: 1, 87: 1, 1943). The Society also offers its bit on post-war problems (**Proc.** 87: 2, 1943). L. T. Morton revives F. H. Garrison's **Medical Bibliography** (Grafton, London, 1943), with the usual omission of recent significant work. Oleanders (Galveston orchids) to Doctor and Mrs. A. F. Hitchcock for their translation of

P. Bert's **Barometric Pressure: Researches in Experimental Physiology** (College Book Company, Columbus, Ohio, 1943).

4. **Antibiotics**: E. Chain, H. W. Florey and Co., give an excellent report on helvolic acid derived from culture filtrates of aspergillus fumigatus (**Brit. J. Exp. Path.**, 24: 108, 1943), with chemical work suggesting the possibility of synthesis of related compounds may be not too complex. Squibb offers a penicillin bibliography and set of abstracts. Squibb's Medical Journal Abstracts are a worthy printed continuance of the successful mimeographed series of long ago.

5. **Etc.**: H. Hurst discusses permeability and molecular constitution as factors in drug action (**Nature**, 152: 292, Sept. 11, 1943). Vale to H. G. Barbour, productive to the end: He made excellent study on water shifts in deep hypothermia (**Amer. J. Physiol.**, 140: 9, 1943). O. R. Klimmer offers a useful discussion of poisoning from combustion gases (**Arch. Exp. Path. Pharmakol.**, 201: 69, 1943). N. G. Yu and Y. Y. Ying state that sternal puncture and the ephedrine provocative test are very helpful in diagnosing chronic malaria (**Chinese Med. J.**, 61: 31, 1943). J. J. Izquierdo offers an excellent discussion of the importance of mathematics in physiology (**Gac. Med. Mexico**, 73: 280, 1943). N. E. Maver and M. K. Barrett show caphepsin difference between tumor and normal tissue (**J. Nat. Cancer**, 4: 65, 1943).

END OF 1943; LET'S MAKE 1944 BETTER!

1. **New Journals**: Welcome to W. B. Cannon & H. E. Sigerist's **American Review of Soviet Medicine**, which got such heavy publicity. 1st issue (October, 1943) has articles on frostbite effect on sympathetics (N. N. Burdenko), time factor in restorative surgery of peripheral nerves (V. V. Lebedenko), & our Mike Shimkin's survey of cancer research in USSR, & P. M. Dawson's account (not in simplifyd spelling) of USSR physical culture. Sleekily elegant, obviously not bothered by restrictions, is **Revista Argentine-Northeamericana de Ciencias Medicas**, offering B. A. Houssay's full review of the role of the pituitary on carbohydrate metabolism (1: 145, 1943) & translated pot-boilers from USA. (N. B.: Very expensive are Argentine medical items: "El Ateneo", Buenos Aires, offers W. T. Fotheringham's 2 vol. **Operaciones Urgentes** for $50, & R. Dassen's **Diagnotico Diferencial Y Tratamiento de las Enfermendades Internas**, 2nd Ed., 774 pp. for $30). Worthy is **Revista do Instituto Adolfo Lutz** (Dept. of Public Health, Sao Paulo), in which F. Almeida & Co. offer a neat review of pathogenic yeast diseases (2: 326, 1942).

2. **Confirmations**: J. Ruiz-Gijon (Madrid) confirms many that dose-effect curve of cat blood pressure effects of epinephrin is hyperbolic (**Arch. Exp. Path. Pharmakol.**, 201: 305, 1943). Also reporting axis-wise is T. Gotsev (Sofia) in confirmation of old J. Blake (**Amer. J. Med. Sc.**, 15: 63, 1848) that magnesium salts lower blood pressure. (**Arch. Exp. Path. Pharmakol.**, 201: 322, 1943). Pal N. David & Co. without benefit of helpful advice confirm (**West. J. Sur. Obs. Gyn.**, 51: 419, 1943) E. Poth & C. Ross's careful work showing phthalylsulfathiazol better than succinylsulfathiazol in handling watery diarrheas (**Fed. Proc.**, 2: 89, 1943, & more fully in winter 1943 issue **Tex. Rep. Biol.**

Med.). H. P. Himsworth **(Lancet,** 245: 465, Oct. 16, 1943) confirms E. B. Astwood **(JAMA,** 122: 78, '43) that thiouea, 3 Gms. daily, greatly benefits cases of thyrotoxicosis. However, J. B. & C. G. MacKenzie **(Proc. Soc. Exp. Biol. Med.,** 54: 34, 1943) find that thiourea tends to cause pulmonary edema in older rats in addition to increasing size of thyroid.

3. **From Instituto Oswaldo Cruz:** Watch G. G. Villela's studies on antitoxic principles from liver **(Rev. Brasil Biol.,** 1: 431, 1941; 2: 365, 1942; 3: 99, 1943; **O Hosp.,** 21: 201, '42). H. Linhares offers evidence on possible insect transmission of leprosy **(Mem. Inst. Oswaldo Cruz,** 38: 321, 1943). M. I. Mello offers rapid chemical test for use in diagnosis of pregnancy on basis of estimation of gonadotropic hormone in urine **(Rev. Brasil Biol.,** 3: 119, 1943).

4. **Anesthesia:** R. M. Waters reviews carbon-dioxide absorption **(Anest.,** 4: 596, 1923). P. S. Ross & R. O. Allen discuss electronarcosis **(Ibid.,** p. 630). F. M. Allen & L. W. Crossman survey refrigeration anesthesia **(Anesth. & Analg.** 22: 264, 1943). N. A. Gillespi **(Ibid.,** p. 275) emphasizes importance of A. E. Guedel's "signs of anesthesia" **(Inhalation Anesthesia, N. Y., 1937).** R. K. Richards & K. Kueter **(Ibid.,** p. 283) confirm R. Beutner & H. Wastl **(Anesth.,** 2: 661, 1943) that calcium salts reduce toxicity of local anesthetic agents.

5. **Et Cetera:** M. L. Tainter proposes methyl cellulose as a colloid laxative **(Proc. Soc. Exp. Biol. Med.,** 54: 77, 1943). J. V. Scudi & M. T. Hamlin report on distribution & slow excretion of atabrine **(Ibid.,** p. 127), but fail to note liver injury following accumulation there. J. H. Gaddum reports on big Faraday Society symposium on drug action **(Nature,** 152: 495, Oct. 30, 1943). J. B. Lippincott, Phila., reprints as book J. C. Aub & Co.'s **Management of Coconut Grove Burns at MGH (Ann. Surg.,** 117, June 1943). G. Brownlee & I. M. Tonkin study acridine powder in wound therapy **(Quart. J. Pharm. & Pharmacol.** 16: 73, 1943). J. H. Gaddum designs toxicity tests in comparison with standards **(Ibid.,** p. 78). M. Maizels discusses physico-chemical changes occurring in stored blood **(Quart. J. Exp., Physiol.,** 32: 143, 1943). R. E. Tunbridge & J. V. Wilson survey pathological & clinical findings in blast injury **(Quart. J. Med.,** 12: 169, 1943). F. M. Burnett & D. R. Bull find influenza virus mutations on chick embryo passage **(Austral. J. Exp. Biol. Med. Sci.,** 21: 55, 1943). D. Engel & E. Forrai **(J. Physiol.,** 102: 127, 1943) find increased capillary permeability in traumatic shock limited sharply to area around trauma. H. J. Seddon & Co. find rate of regeneration of peripheral nerves in man after suture to be about 1.5 mm. per day **(Ibid.,** p. 191). B. Gerstl & R. Tennant explore enzymes as factors in resistance to TB **(Yale J. Biol. Med.,** 16: 1, 1943). Merck & Co. also issue a bibliography on penicillin & other anti-biotics.

1943 SUPPLEMENT—HERE'S TO 1944!

1. **Antibiotics:** Of utmost importance is report by Harold Raistrick & Co. of London School of Hygiene & Tropical Medicine on "Patulin in the Common Cold: Collaborative Research on a Derivative of Penicillium Patulum Bainier" **(Lancet,** 245: 625-635, Nov. 20, 1943).

Patulin forms white crystals melting at 111° C. & is anhydro-3-hydroxymethylene-tetrahydro-y-pyrone-2-carboxylic acid, with bacteriostatic action vs. various organisms in dilutions of 1:33,00 to 1:80,000, & LD50 for mice of 25 Gms/Kg IV. W. E. Gye & W. A. Hopkins find it effective in common cold applied locally in buffered phosphate sol. 1:20,000, with Maj. Greenwood's comment on statistical significance of treated vs. untreated controls. Now, to synthesize penicillin. Congratulations!

2. **Biochemorphology:** This word, now properly dictionaried, need not be feared for use! W. D. Kumler & T. C. Daniels show that chief factor for activity of sulfonamides is the reasonating form with coplanar amino group & negative sulfone group (**J. Am. Chem. Soc.**, 65: 2190, 1943). P. Gyorgy & Co. find sulfhydryl compounds retard oxidation of fats only in presence of water, maybe explaining hypometabolic effects of sulfonamides & thicureas & synergism between p-aminobenzoic & sulfonamides on reducing rat thyroid & retarding rancidity of fat (**Science**, 98: 518, Dec. 10, 1943). F. B. Rodman & H. N. Wright survey colloid properties of arsphenamines in relation to distribution & retention of tissues (**J. Pharmacol. Exp. Therap.**, 79: 140, 1943). O. H. Robertson & Co. find propylene glycol bactericidal in conc. of 1 Gm per 5 million cc air (**J. Exp. Med.**, 78: 387, 1943).

3. **Climate:** K. K. Chen & Co. show that drug toxicity increases with rise in temperature along with increase in rate of action (**J. Pharmacol. Exp. Therap.**, 79: 127, 1943). W. F. Petersen entertains with interesting account of weather on Lincoln, Douglas, and Mary Todd Lincoln (**Lincoln-Douglas: The Weather as Destiny**, C. C. Thomas, Springfield, Ill., 1943).

4. **Pain.** H. G. Wolff & C. Torda show increase in urinary excretion of 17-ketosteroids during migraine, maybe related to similar increase in stress (**J. Clin. Invest.**, 22: 853, 1943; G. Pincus, **J. Clin. Endocrin.**, 3: 195, 1943). Just out is excellent volume on **Pain**, from Association for Research in Nervous & Mental Disease (Wms. & Wilkins, Balt., 1943).

5. **Cancer:** Whole October issue **Journal National Cancer Institute** (2: 131-248, 1943) is devoted to W. R. Earle's keen studies on production of malignancy **in vitro**. O. M. Q. Cantuarias emphasized adrenal cortex in new experimental approach to cancer (**Rev. Med. Exper.**, Lima, 2: 131, 1943).

6. **Etc.:** S. Wolf offers neat study showing that nausea occurs only during gastric relaxation & Hypomotility following various nauseating stimuli, & may be prevented by giving combination of 15 mgm prostigmine HBr & 1.2 mgm atropine sulfate, which induces stomach contractions (**J. Clin. Invest.**, 22: 877, 1943). Prevents seasickness? I. Chavez & Co., of Mexico City, find that liver function is impaired in various kinds of cardiac insufficiency somewhat in proportion to degree of heart involvement. (**Arch. Lat. Amer. Card. Hematol.**, 13: 51, 1943). F. S. Daft & W. H. Sebrell report successful treatment of granulocytopenia & leukemia in rats with folic acid. (**Pub. Health Rep.**, 58: 1542, 1943). L. Dexter & Co. (**J. Clin. Invest.**, 22: 847, 1943) confirm E. Ogden & Co. that renal humoral pressor mechanism compensates for

hemorrhage hypotension (**Proc. Soc. Exp. Biol. Med.**, 48: 505, 1941). E. Braun-Menendez & Co., ousted for freedom loving in Argentina, offer logical nomenclature for renal humoral pressor agents (**Science**, 98: 495, Dec. 5, 1943). We assume everyone reads **JAMA**, but did you note Council on Pharmacy & Chemistry's report on the metric system (**JAMA** 123: 900, Dec. 4, 1943) & subsequent editorials & comments? Come on, docs, let's be sensible and learn to use it. Maybe you also noted O. Baudisch's survey of trace elements (Ibid. p. 959, Dec. 11, 1943).

Here's to a successful & satisfying New Year!

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TEXAS REPORTS ON BIOLOGY AND MEDICINE

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